UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC. and YEDA RESEARCH AND DEVELOPMENT CO. LTD., *Plaintiffs*, v. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG, and MOMENTA PHARMACEUTICALS, INC., *Defendants*.	Civil Action No. 08-CV-7611 (BSJ) (AJP) ECF Case
TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., *Plaintiffs*, v. MYLAN PHARMACEUTICALS INC., MYLAN INC., and NATCO PHARMA LTD., *Defendants*.	Civil Action No. 09-CV-8824 (BSJ) (AJP) ECF Case **DEFENDANTS SANDOZ INC. AND MOMENTA PHARMACEUTICALS, INC.'S OPPOSITION TO PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW** **(HIGHLY CONFIDENTIAL AND EXTERNAL COUNSEL ONLY – FILED UNDER SEAL PURSUANT TO PROTECTIVE ORDER)**

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OTHER AUTHORITIES

I. BACKGROUND OF THE CASE

A. The Parties

Sandoz's Response:

Sandoz does not dispute any of Teva's proposed findings Nos. 1-9.

1. Plaintiff and counterclaim-defendant Teva USA is a Delaware corporation with its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454-1090. (No. 08-cv-7611, Dckt. No. 271 ("Stipulations"), ¶ 55.)

2. Plaintiff and counterclaim-defendant Teva Ltd. is an Israeli company with its principal place of business at 5 Basel Street, P.O. Box 3190, Petah Tikva, 49131, Israel. (Stipulations, ¶ 56.)

3. Plaintiff and counterclaim-defendant Teva Neuroscience is a Delaware corporation with its principal place of business at 901 E. 104th Street, Suite 900, Kansas City, MO 64131. (Stipulations, ¶ 57.)

4. Plaintiff and counterclaim-defendant Yeda markets and commercializes new developments emerging from the laboratories of the Weizmann Institute of Science ("Weizmann Institute"), and its principal place of business is at P.O. Box 95, Rehovot, 76100, Israel. (Stipulations, ¶ 58.)

5. Defendant and counterclaim-plaintiff Mylan Pharmaceuticals Inc. is a wholly-owned subsidiary of Mylan Inc. (referred to together as "Mylan") and a corporation organized under the laws of the State of West Virginia, having an office and place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505. (Stipulations, ¶ 59.)

6. Defendant and counterclaim-plaintiff Mylan Inc. is a corporation organized under the laws of the Commonwealth of Pennsylvania, having an office and place of business at 1500 Corporate Drive, Canonsburg, Pennsylvania 15317. (Stipulations, ¶ 60.)

7. Defendant and counterclaim-plaintiff Natco Pharma Ltd. ("Natco") is an Indian company with its principal place of business at Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033, India. (Stipulations, ¶ 61.)

8. Defendant and counterclaim-plaintiff Sandoz Inc. ("Sandoz") is a Colorado corporation with its principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540. (Stipulations, ¶ 62.)

9. Defendant and counterclaim-plaintiff Momenta Pharmaceuticals, Inc. ("Momenta") is a Delaware corporation with its principal place of business at 675 West Kendall Street, Cambridge, Massachusetts 02142. (Stipulations, ¶ 63.)

B. The Patents-in-Suit

Sandoz's Response:

Sandoz does not dispute any of Teva's proposed findings Nos. 10-11.

10. The patents-in-suit are U.S. Patent Nos. 5,981,589 ("the'589 Patent"), 6,054,430 ("the'430 Patent"), 6,342,476 ("the'476 Patent"), 6,362,161 ("the'161 Patent"), 6,620,847 ("the'847 Patent"), 6,939,539 ("the'539 Patent") and 7,199,098 ("the'098 Patent") (collectively, "the Orange Book Patents") and U.S. Patent Nos. 5,800,808 ("the'808 Patent") and 6,048,898 ("the'898 Patent") (collectively with the Orange Book Patents, the "patents-in-suit"). (Stipulations, ¶ 64.)

11. Each of the patents-in-suit is entitled "Copolymer-l improvements in compositions of copolymers." (Stipulations, ¶ 67.) The four inventors named on the patents-in-suit are Eliezer Konfino, Michael Sela, Ruth Arnon, and Dvora Teitelbaum. (PTX 1-9.) Eliezer Konfino worked for Teva and retired from the company in December 1991. Michael Sela, Ruth Arnon, and Dvora Teitelbaum worked at the Weizmann Institute. (Stipulations, ¶ 66.)

C. Copaxone® – Teva NDA

Sandoz's Response:

Sandoz does not dispute any of Teva's proposed findings Nos. 12-13 or 15-19.

12. Teva USA is the holder of New Drug Application ("NDA") No. 20-622, for glatiramer acetate, which was approved by the FDA on December 20, 1996. (Stipulations, ¶¶ 82, 83.)

13. Teva markets and sells glatiramer acetate under the tradename Copaxone® in the United States. (Stipulations, ¶ 84.)

14. Glatiramer acetate is a form of copolymer-1. (Sept. Tr. (Grant) 220:13-221:2; Sept. Tr. (Owens) 630:11-631:8; PTX 206 at SDZ00000031; PTX 320 at MYL0000236.)

Sandoz's Response:

Glatiramer acetate is not merely a form of copolymer-1. The phrase "glatiramer acetate" is interchangeable with "copolymer-1." (DTX 1738 at KRULL0000023 ("Originally known as 'Copolymer-1' or 'Cop-1,' glatiramer acetate was discovered in the 1960s by Israeli scientists at the Weizmann Institute.")); (PTX 3563 at TEV000104078 ("COPAXONE® is the brand name for glatiramer acetate (formerly known as copolymer-1.").)

D. Sandoz/Momenta's ANDA

Sandoz's Response:

Sandoz does not dispute any of the proposed findings within Nos. 20-22, but objects to the extent Teva is implying that Sandoz's proposed glatiramer acetate product was developed solely between June 2007 and December 2007. Momenta and Sandoz started much earlier than Teva suggests. The Court should make these additional findings:

SDZ341. Momenta Pharmaceuticals, Inc. became interested in making a generic version of Copaxone in late 2004 and early 2005. (Sept. Tr. at 1068:1-6 (Brugger).) Work on the project began in 2005. (PTX 957 at 19:12-16 (Brugger).) By July 5, 2006, Momenta had filed a patent application directed to an "Improved Process for the Preparation of Copolymer-1. (PTX 177.)

SDZ342. Momenta and Sandoz began considering a collaboration to make a proposed glatiramer acetate product as early as February 2005. (PTX 119; PTX 957 at 74:19-75:2) (Brugger).) By October 2006, Momenta and Sandoz had formally kicked off the collaboration with Momenta sharing its ideas with Sandoz regarding how to make a proposed glatiramer acetate product. (PTX 157; PTX 957 at 95:18-96:15) (Brugger).)

20. Momenta entered into a collaboration and license agreement with Sandoz AG on June 13, 2007, regarding, among other things, the development of a generic Copaxone® product. (PTX 957 (Brugger Dep.) at 105:12-106:08; PTX 175.)

21. Sandoz submitted an abbreviated new drug application ("ANDA"), No. 90-218, on December 27, 2007, seeking approval from the FDA to manufacture and sell a generic Copaxone® product before the expiration of the Orange Book Patents. (Stipulations, ¶¶ 92, 93.)

22. [redacted]

Sandoz's Response:

[redacted]

23. [redacted] The Briefing Book, among other things, described at a high level certain changes that might be made to Sandoz's manufacturing process. (PTX 913.) To date, however, no amendment to Sandoz's ANDA has been filed that makes any of the changes that the Briefing Book proposed.

Sandoz's Response:

The Court should make these additional findings of fact:

SDZ343. The Briefing Book is not a "high level" document describing things that might happen. It is a 63-page update, informing the FDA of changes Momenta has actually made to its proposed glatiramer acetate product and the process of making the product. [redacted]

SDZ344. Because the Sandoz ANDA would not be approved by the FDA without changes, Momenta amended its ANDA so it will be accepted by the FDA. The

[redacted] including changes affecting both the molar ratio of the proposed product and the use of a viscometer as an in-process control:

[redacted]

> (1) Process Changes for the Manufacture of Glatiramer Acetate: The scale for the manufacture of drug substance has been increased from approximately [redacted] (Process 1.0.0) to [redacted] (Process 1.1.0). While this is a modest increase in scale, <u>results from Quality by Design (QbD) experiments have revealed key aspects related to both the kinetics and the amino acid ratio/charge</u> that are integral to questions posed by the FDA in deficiency questions.
>
> (2) Enhanced Process Controls for the Manufacture of Glatiramer Acetate: In addition to the process controls already presented to the [redacted] controls have been developed and incorporated. <u>This includes an In-Process Control method for the depolymerization reaction in Step 2 for control of molar mass.</u> The additional controls are targeted to assure both a reproducible process and equivalence to the reference listed drug.
>
> (3) Characterization of Glatiramer Acetate: There have been several updates to key analytical methods [redacted] that have enhanced our ability to demonstrate equivalence with the RLD as well as control the manufacture of Glatiramer Acetate.

(PTX 913 at 5.)

SDZ345. Dr. John Bishop, Momenta's Vice President for Pharmaceutical Sciences, testified about the Briefing Book and the changes to the molar ratio specification and the use of a viscometer as an in-process control. Specifically, Dr. Bishop testified that the Briefing Book reflected the amino acid content specification that Momenta intends to use in its proposed glatiramer acetate product. (Sept. Tr. 1093:17-1096:4.) He also testified that Sandoz informed that FDA in the Briefing Book that it has

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implemented a viscosity test to measure the time of the reaction in Step 2 of the manufacturing process. (Sept. Tr. 1099:21-1103:24-1105:11; PTX 913 at 38.)

SDZ346. The Court granted Teva's request for additional discovery regarding [redacted] before trial. (No. 08-cv-7611, D.I. 266.) Teva took Dr. Bishop's deposition in response to the Court's order. Teva used its deposition to explore whether the changes described in the Briefing Book were actually implemented at Momenta:

> [T]he only issue that Mr. Bishop was deposed on is what information have they given the FDA, what have they told the FDA about the process. You know the issue was what are they actually going to be using or is it just tentative or is this real?

(Sept. Tr. 1103:17-21.)

SDZ347. Teva did not give the Court any reason to find that Dr. Bishop's testimony was not credible. The Court finds that Dr. Bishop's testimony was credible and that, if approved by the FDA, Sandoz's glatiramer acetate product will have the characteristics described in the Briefing Book and will be made using the viscosity in-process control described in the Briefing Book.

E. Commencement of Sandoz/Momenta Lawsuit

Sandoz's Response:

Sandoz does not dispute any of the proposed findings within Nos. 24-26, but objects to the extent that they paint an incomplete picture of the pleadings in this case. Teva's Complaint also included an allegation that its patented invention is so complex and secret that Sandoz could not possibly have developed a generic Copaxone product unless Sandoz had stolen Teva's trade secret information. (No. 08-cv-7611, D.I. 1, Complaint, ¶¶ 67-89.) Teva's theory was that

originally named Defendant Novartis AG stole Teva's trade secrets through its acquisition of Teva's former Copaxone distributor in Slovenia, provided the trade secrets to another original Defendant, Germany-based Sandoz International GmbH, which, in turn, provided the trade secret information to New Jersey-based Sandoz Inc., which used the information to develop its product and file an ANDA for a generic Copaxone. (*Id.*) At trial, Teva presented a completely different theory, namely that its patents enabled those of ordinary skill in the art to make the claimed invention without undue experimentation.

24. Sandoz filed with the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the claims of the Orange Book Patents are invalid, unenforceable, and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Sandoz's ANDA proposed glatiramer acetate product ("Paragraph IV Certification"). (Stipulations, ¶ 94.)

25. Sandoz sent a letter ("the Notice Letter"), dated July 10, 2008, to Teva USA, Teva Ltd., Teva Neuroscience and Yeda, notifying them that Sandoz Inc. had filed an ANDA for glatiramer acetate and was providing information to Teva pursuant to 21 U.S.C. § 355(j)(2)(B)(i)-(ii). (Stipulations, ¶ 95.)

26. On August 28, 2008, Teva and Yeda sued Sandoz and Momenta (collectively "Sandoz" or the "Sandoz Defendants") for infringement of the Orange Book Patents in the action captioned *Teva Pharmaceuticals USA, Inc., et al. v. Sandoz Inc., et al.*, C.A. No. 08-cv-7611 (S.D.N.Y.). (Stipulations, ¶ 97.)

27. The Sandoz Defendants counterclaimed for, *inter alia*, a declaratory judgment of non-infringement, invalidity and unenforceability of the '808 and '898 Patents. (No. 08-cv-7611, D.I. 14 at ¶¶ 89-116, D.I. 16 at ¶¶ 89-116.)

Sandoz's Response:

SDZ348. Sandoz also counterclaimed for a declaratory judgment of non-infringement, invalidity and unenforceability of the '589, '476, and '161 Patents. (No. 08-cv-7611, D.I. 14 at ¶¶ 44-88, D.I. 16 at ¶¶ 44-88.)

F. Mylan/Natco ANDA

Sandoz's Response:

Sandoz takes no position on Teva's allegations regarding the Mylan/Natco ANDA.

28. Natco and Mylan have signed an agreement dated June 7, 2008, relating to the development and marketing of a glatiramer acetate product in the United States. (Stipulations, ¶ 87; PTX 245.)

29. On June 29, 2009, Mylan submitted an ANDA, No. 91-646, seeking approval to manufacture and sell Mylan's proposed glatiramer acetate product before the expiration of the Orange Book Patents. (Stipulations, ¶¶ 86, 88.)

30. [redacted]

31. On April 19, 2011, Mylan submitted a major amendment to its ANDA. (DTX 1411.) Mylan's major amendment did not make any changes to its manufacturing process.

G. Commencement of Mylan/Natco Litigation

Sandoz's Response:

Sandoz takes no position on Teva's allegations regarding the commencement of the Mylan/Natco litigation.

32. Mylan filed with the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the claims of the Orange Book Patents are invalid, unenforceable, and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Mylan's proposed glatiramer acetate product ("Paragraph IV Certification"). (Stipulations, ¶ 89.)

33. Mylan sent a notice letter, dated September 16, 2009, to Teva USA, Teva Ltd., Teva Neuroscience and Yeda, notifying them that Mylan had filed an ANDA for glatiramer acetate and was providing information to Teva pursuant to 21 U.S.C. § 355(j)(2)(B)(ii). (Stipulations, ¶ 90.)

34. On October 16, 2009, Teva and Yeda sued Mylan, Mylan, Inc., and Natco Pharma Ltd. (collectively "Mylan" or the "Mylan Defendants") for infringement of the Orange Book Patents in the action captioned *Teva Pharmaceuticals USA, Inc., et al. v. Mylan Pharmaceuticals, Inc., et al.*, C.A. No. 09-cv-8824 (S.D.N.Y.). (Stipulations, ¶ 91.)

35. The Mylan Defendants counterclaimed for, *inter alia*, a declaratory judgment of non-infringement and invalidity of the '808 and '898 Patents. (No. 09-cv-8824, D.I. 8 at ¶¶ 82-117, D.I. 34 at ¶¶ 187-224.)

H. Procedural History of the Cases

Sandoz's Response:

Sandoz takes no position on Teva's recitation of the procedural history of the case other than that it omits Teva's admission that its Slovenian trade secret theft allegations were unfounded, forcing it to drop the allegations, but not until over a year after making the allegations in its complaint. (No. 08-cv-7611, D.I. 85.)

36. Plaintiffs and the Sandoz Defendants submitted claim construction briefing in October to December 2009, and a claim construction hearing was held on January 20, 2010. (No. 08-cv-7611, D.I. 68-72; D.I. 76-82; D.I. 89-93, 96-97; D.I. 102, 104-105; D.I. 114-119.)

37. The Sandoz Defendants moved for summary judgment of indefiniteness on December 23, 2009. (No. 08-cv-7611, D.I. 120-122.) Plaintiffs opposed the Sandoz Defendants' motion. (No. 08-cv-7611, D.I. 128.) In connection with their opposition, Plaintiffs submitted declarations from experts Dr. Gregory Grant and Dr. Paul Dubin. (No. 08-cv-7611, D.I. 127, 128.3.) The Sandoz Defendants subsequently moved to strike the declarations of Dr. Grant and Dr. Dubin on *Daubert* grounds. (No. 08-cv-7611, D.I. 144, 148.) On September 7, 2010, the Court denied the Sandoz Defendants' motion for summary judgment and motion to strike Dr. Grant's and Dr. Dubin's declarations. (No. 08-cv-7611, D.I. 181 at 4, 9, 11, 13.)

38. Following the denial of the Sandoz Defendants' motion for summary judgment of indefiniteness, Plaintiffs and the Sandoz Defendants submitted supplemental briefing on the Sandoz Defendants' proposed construction of the term "average molecular weight." (No. 08-cv-7611, D.I. 192-193, 204-206.)

39. On October 22, 2010, the Court ordered that the *Sandoz* and *Mylan* cases be consolidated. (No. 08-cv-7611, D.I. 200.)

40. Plaintiffs and the Mylan Defendants submitted claim construction briefing in April to July 2010. (No. 09-cv-8824, D.I. 38-39, 41; D.I. 43-45; D.I. 57-65.) The Mylan Defendants moved for summary judgment of indefiniteness on November 15, 2010. (No. 09-cv-8824, D.I. 96-98.)

41. On August 24, 2011, the Court issued a Memorandum and Order (No. 08-cv-7611, D.I. 273; No. 09-cv-8824, D.I. 194) ("Claim Construction Order") denying Mylan's motion for summary judgment of indefiniteness and construing the disputed claim terms as follows:

- "Copolymer-1" has been construed as "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively, non-uniform with respect to molecular weight and sequence, which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides." Claim Construction

Order at 12.)

- "Average molecular weight" has been construed as "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (Claim Construction Order at 40.)

- "Copolymer-1 having a molecular weight" has been construed as "copolymer-1 having a peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (Claim Construction Order at 40, n.10.)

- "Polypeptides composed of glutamic acid, lysine, alanine and tyrosine" has been construed as "more than one polypeptide, each consisting essentially of glutamic acid, lysine, alanine and tyrosine residues." (Claim Construction Order at 14-15.)

- "Copolymers of alanine, glutamic acid, lysine and tyrosine" is construed to mean "more than one polymer molecule, each consisting essentially of glutamic acid, lysine, alanine and tyrosine residues." (Claim Construction Order at 15.)

- "Copolymer-l fraction" has been construed as "a portion of a copolymer-1 mixture having a narrower molecular weight distribution than the starting protected copolymer-l mixture." (Claim Construction Order at 16.)

- "Toxicity" has been construed as "the degree to which a substance exhibits negative effects in mouse mortality or RBL degranulation test." (Claim Construction Order at 44.)

- "Predetermined" has been construed to mean "determined beforehand." (Claim Construction Order at 47.)

- "Predetermined by a test reaction" has been construed as "determined beforehand by a reaction carried out to determine results of varying reaction conditions." Claim Construction Order at 50.)

(i) <u>July Trial</u>

42. Starting on July 11, 2011, the Court held a trial on Defendants' inequitable conduct defense. The Court heard live testimony from the following witnesses:

(1) Plaintiffs' Witnesses

Dr. Irit Pinchasi

Sandoz's Response:

Sandoz responds that the entirety of Dr. Pinchasi's trial testimony, including her cross examinations, should serve as the proper description of her testimony. *See also* Sandoz's Opening FFCOL ¶ 73, 308-312.

43. Dr. Irit Pinchasi is a former Vice President for Innovative R&D at Teva. (July Tr. (Pinchasi) 13:13-17.) She was awarded a Ph.D. in biochemistry from Tel Aviv University in 1984, and did post doctoral work at the Weizmann Institute of Science (the "Weizmann Institute"). (July Tr. (Pinchasi) 8:19-9:11.)

44. Dr. Pinchasi testified regarding the research and development of Teva's Copaxone® product; the inventions described in the patents-in-suit; the technology related to those inventions; and Teva's initial patent application filed in May 1994.

Professor Ruth Arnon

Sandoz's Response:

Sandoz responds that the entirety of Dr. Arnon's trial testimony, including her cross examinations, should serve as the proper description of her testimony. Sandoz objects to the extent that Teva's proposed findings omit that before Professor Arnon was named as an inventor of the patents-in-suit, she was also (1) a co-author of the 1971 Teitelbaum article that first described copolymer-1 appearing in the European Journal of Immunology (PTX 499); (2) an inventor on the first patent describing copolymer-1, U.S. Patent No. 3,849,550 (PTX 26); and (3) a co-author of the 1987 *New England Journal of Medicine* article reporting the results of the BR-1 Bornstein copolymer-1 clinical trial. (PTX 31.) Accordingly, the Court should make these additional findings:

SDZ349. Professor Arnon was not named as an inventor of the patents-in-suit on the night that the original patent application was filed. (PTX 11 at TEV000309434.)

SDZ350. Professor Arnon was a co-author of the 1971 Teitelbaum article that first described copolymer-1 appearing in the *European Journal of Immunology* (PTX 499).

SDZ351. Professor Arnon was an inventor on the first patent describing copolymer-1, U.S. Patent No. 3,849,550 (PTX 26).

SDZ352. Professor Arnon was a co-author of the 1987 *New England Journal of Medicine* article reporting the results of the BR-1 Bornstein copolymer-1 clinical trial. (PTX 31.)

45. Professor Ruth Arnon is a named inventor on the patents-in-suit. (PTX 1.) She is currently Professor Emeritus at the Weizmann Institute and President of the Israel Academy of Sciences and Humanities. (July Tr. (Arnon) 303:14-17.) She was formerly Chairman of the Department of Chemical Immunology, Dean of the Faculty of Biology, and Vice President of the Weizmann Institute. (July Trial Tr. (Arnon) 307:16-21.)

46. Professor Arnon was awarded a Ph.D. in biochemistry from the Weizmann Institute of Science in 1960 and then completed post-doctoral studies at the Rockefeller University in New York. (July Tr. (Arnon) 305:3-7, 306:24-307:1.)

47. Professor Arnon has over 400 publications in immunology and biochemistry, and has been awarded numerous prizes in that field, including the Robert Koch Prize for Medical Sciences (Germany), the Jiminez Diaz Award for Medical Research (Spain), the Wolf Prize (international), the Israel Prize, and the Rothschild Prize (Israel). (July Tr. (Arnon) 308:3-17.) Professor Arnon is a Chevalier of the Legion D'Honneur (France) and is an elected member of the American Philosophical Society. (July Tr. (Arnon) 308:3-17.)

48. Professor Arnon testified regarding the discovery and development of copolymer-1; the inventions of the patents-in-suit; the technology related to those inventions and the initial patent application filed in May 1994.

Dr. Barbara Baird

Sandoz's Response:

Sandoz responds that the entirety of Dr. Baird's trial testimony, including her cross examinations, should serve as the proper description of her testimony and that any finding regarding her expertise should be based only on the specific subject matter for which the Court accepted Dr. Baird at trial.

49. Dr. Barbara Baird is the Horace White Professor and Chair of the Department of Chemistry and Chemical Biology at Cornell University. (July Tr. (Baird) 569:7-11; PTX 768.)

50. Dr. Baird was awarded a Ph.D. in chemistry from Cornell University in 1979 and was a Damon Runyon Walter Winchell Cancer Fund Fellow at the National Institutes of Health ("NIH") in the immunology branch of the National Cancer Institute. (July Tr. (Baird) 571:3-10; PTX 768.)

51. Dr. Baird is an expert in the rat basophilic leukemia ("RBL") degranulation test, and has been using the RBL test for over 30 years. (July Tr. (Baird) 572:7, 573:6-14, 576:10-12, 585:22-586:1.)

52. Dr. Baird has authored approximately 140 publications. (July Tr. (Baird) 573:15-20; PTX 769.) She has received numerous awards, including the Harold Lamport Award for Biophysics and Physiology from the New York Academy of Sciences and a National Science Foundation award for women in science and engineering. (July Tr. (Baird) 574:8-20; PTX 768.) Dr. Baird was a Guggenheim Fellow, and is a member of the American Association for the Advancement of Science in both chemistry and biology and the American Academy of the Arts and Sciences. (July Tr. (Baird) 574:8-20.)

53. Dr. Baird testified regarding the RBL degranulation test and its use by the Weizmann Institute and Teva, including in the patents-in-suit.

(2) Defendants' Witnesses

Dr. Ian Kimber

54. Dr. Ian Kimber is the chairman of the Department of Toxicology at the University of Manchester. He testified regarding toxicity testing described in the patents-in-suit.

Sandoz's Response:

The Court should make these additional finding regarding Dr. Kimber:

SDZ353. Dr. Kimber was Principal Fellow and Head of Research at Syngenta Central Toxicology Laboratory in Macclesfield, England. (July Tr. 367:18-22, 368:5-10; DTX 1321.) At Syngenta, Dr. Kimber's research covered immunology and toxicology, with a particular focus on the regulation of immune responses and allergic disease. (July Tr. 368:17-20.)

SDZ354. Dr. Kimber received both his Masters of Science and his Ph.D. from the University of Manchester. (July Tr. 368:24-369:1; DTX 1321.)

SDZ355. Since the early 1990s, he has served on advisory boards and industry panels for such organizations as the United Kingdom's Medical Research Council and Ministry of Defence, as well as the World Health Organization, with a particular emphasis on immunotoxicology issues. (July Tr. 370:11-21; DTX 1321.)

SDZ356. Dr. Kimber serves on advisory panels for Procter & Gamble, PepsiCo Europe, Roche Pharmaceuticals, and AstraZeneca Pharmaceuticals. (July Tr. 370:6-10.) He also serves on the editorial boards of several peer-reviewed publications, such as the "Journal of Immunotoxicology and Journal of Immunology." (July Tr. 370:22-371:8.)

SDZ357. Dr. Kimber has written or co-authored over 650 publications, including 450 peer-reviewed articles and over 100 book chapters. (July Tr. 369:16-19; DTX 1321.) He was recently awarded the OBE, or Officer of the Order of the British Empire, for services to science. (July Tr. 371:17-24.)

(*See also* Sandoz's Post-Trial Proposed Findings of Fact and Conclusions of Law ("Sandoz's Opening FFCOL") ¶¶ 271-75.)

Eugene Rzucidlo

55. Mr. Eugene Rzucidlo is an attorney at the law firm Hershkovitz & Associates. Mr. Rzucidlo testified regarding the process of patent prosecution and the prosecution histories of the patents-in-suit.

<u>*Sandoz's Response:*</u>

The Court should make this additional finding regarding Mr. Rzucidlo:

SDZ358. Mr. Eugene C. Rzucidlo provided the Court an overview of the prosecution history of the patents-in-suit. Mr. Rzucidlo obtained his Bachelor of Science in Chemistry degree in 1963. He taught courses in chemistry and later worked as a research chemist until 1970. (July Tr. 496:19-497:22.) In 1970, he became a patent examiner at the PTO; and after four years, he became a primary patent examiner. (July Tr. 497:23-498:10.) Mr. Rzucidlo worked in PTO Art Group 140, which was responsible for examining patent applications related to polymers. (July Tr. 498:14-17.) He later became a member of the Board of Patent Appeals, serving in that position until he left the PTO in 1985. (July Tr. 498:24-499:8.) He has practiced before the PTO continuously since 1985. (July Tr. 499:16-500:11.)

(*See also* Sandoz Opening FFCOL ¶ 314.)

(ii) <u>September Trial</u>

56. Starting on September 7, 2011, the Court held a trial on Plaintiffs' infringement claims and Defendants' non-infringement and invalidity defenses. The Court heard testimony from Sandoz on its non-infringement, obviousness, and lack of enablement and indefiniteness defenses. The Court heard testimony from Mylan on its non-infringement, best mode, and obviousness defenses. At trial, Mylan presented no evidence on lack of enablement or indefiniteness and Sandoz presented no evidence on best mode. During the trial, Mylan notified Plaintiffs and the Court that it was no longer asserting that the patents are invalid based on anticipation or public use. (Sept. Tr. 1349:9-1351:24.)

Sandoz's Response:

Teva continues to pretend that counsel for Sandoz and Mylan did not share responsibilities for presenting some of the defenses. It is wrong to say that "Mylan presented no evidence on lack of enablement or indefiniteness and Sandoz presented no evidence on best mode." Teva complained before trial that the defendants would duplicate one another with overlapping experts and argument. The Defendants agreed to avoid repetition. Now, Teva suggests that particular defenses lack merit because lawyers for both sets of Defendants did not present the evidence on these defenses.

57. At the September trial, the Court heard live testimony from the following witnesses:

(1) Plaintiffs' Witnesses

Jon Congleton

58. Mr. Jon Congleton is the Senior Vice President and General Manager of Teva Neuroscience. (Sept. Tr. (Congleton) 39:19-22.) He has been with Teva Neuroscience for over 15 years. (Sept. Tr. (Congleton) 41:12-13.) Prior to becoming Senior Vice President, Mr. Congleton served as both product director and director of marketing for Copaxone®. (Sept. Tr. (Congleton) 42:1-13.)

Sandoz's Response:

Undisputed.

59. Mr. Congleton testified regarding the nature of Teva's business, sales and marketing of Copaxone®, and the history and state of the market for multiple sclerosis treatments.

Sandoz's Response:

Undisputed.

Dr. Robert Lisak

Sandoz's Response:

Sandoz responds that the entirety of Dr. Lisak's trial testimony, including his cross examinations, should serve as the proper description of his testimony and that any finding regarding his expertise should be based only on the specific subject matter for which the Court accepted Dr. Lisak at trial. Sandoz objects to the extent that Teva's proposed findings omit that Dr. Lisak admitted that, as a principal investigator of the Johnson 9001 copolmer-1 clinical trials, he had no idea that Teva was purportedly using his clinical study to determine a correlation between lower molecular weight and lower toxicity. [DTX 3511 (Lisak Depo. 82:3-89:14, 100:8-106:4.) With the exception of a declaration created for and submitted to the PTO, there is not a single document showing that Teva conducted the Johnson 9001 trials to test whether lower molecular weight of copolymer-1 exhibited reduced toxicity between the time of the Bornstein BR-1 trial and the Johnson 9001 trial.

60. Dr. Robert Lisak has been the Chairman of the Department of Neurology and Professor of Immunology and Microbiology at Wayne State University for the past 25 years. He is also Chief of Neurology at Harper University Hospital. (Sept. Tr. (Lisak) 78:6-79:7, 84:6-11; PTX 419.)

61. Dr. Lisak received his M.D. from the College of Physicians and Surgeons of Columbia University in 1965, and conducted two years of research related to multiple sclerosis at the National Institutes of Mental Health. (Sept. Tr. (Lisak) 82:6-11, 15-17; PTX 419.)

62. Dr. Lisak is an expert in multiple sclerosis and its treatment. (Sept. Tr. (Lisak) 87:24-88:6.) He has been treating multiple sclerosis patients since 1972, and personally treats about 500 MS patients currently. (Sept. Tr. (Lisak) 79:23-80:4.) Dr. Lisak has evaluated and treated about 4,500 to 5,000 multiple sclerosis patients in his career. (Sept. Tr. (Lisak) 80:5-7.)

63. Dr. Lisak has received numerous awards including a Lifetime Achievement Award from the Consortium of Multiple Sclerosis Centers and a Doctor's Award from the Myasthenia Gravis Foundation of America. (Sept. Tr. (Lisak) 86:3-12, 86:17-87:5; PTX 419.) He was elected as an honorary member of the American Neurologic Association, and a fellow by distinction of the Royal College of Physicians of London. (Sept. Tr. (Lisak) 86:3-12; PTX 419.)

64. Dr. Lisak has published over 220 papers, in addition to reviews, book chapters,

and editorials. (Sept. Tr. (Lisak) 81:3-9.) He is the editor-in-chief of the *Journal of Neurological Sciences* and is on the editorial board of the journal *Clinical Neuropharmacology*. (Sept. Tr. (Lisak) 84:12-20.)

65. Dr. Lisak was the principal investigator at Wayne State University for the first large-scale clinical study of copolymer-1 for the treatment of relapsing-remitting multiple sclerosis. (Sept. Tr. (Lisak) 106:24-107:10; PTX 597.) He was also a co-author on the study publication, Johnson, *et al.*, Copolymer 1 Reduces Relapse Rate and Improves Disability in Relapsing-Remitting Multiple Sclerosis: Results of a Phase III Multi-Center, Double-Blind, Placebo-Controlled Trial, *Neurology*, 45:1268-76 (1995). (Sept. Tr. (Lisak) 108:5-17; PTX 597.)

66. At the time the application that led to the patents-in-suit was filed in May 1994, Dr. Lisak had been treating multiple sclerosis patients for over twenty years. Dr. Lisak testified regarding the disease of multiple sclerosis and its treatment; the long felt need for a drug like Copaxone®; the failure of others to develop safe and effective treatments for multiple sclerosis; and Defendants' infringement of claim limitations relating to treatment of multiple sclerosis.

Dr. Gregory Grant

Sandoz's Response:

Sandoz responds that the entirety of Dr. Grant's trial testimony, including his cross examinations, should serve as the proper description of his testimony and that any finding regarding his expertise should be based only on the specific subject matter for which the Court accepted Dr. Grant at trial.

67. Dr. Gregory Grant is a Professor of Biochemistry in Medicine and Developmental Biology at the School of Medicine at Washington University School of Medicine. (Sept. Tr. (Grant) 178:9-13; PTX 760.) He is also Director of the Protein and Nucleic Acid Chemistry Laboratories of Washington University. (Sept. Tr. (Grant) 178:14-17; PTX 760.)

68. Dr. Grant is an expert in the characterization of proteins and polypeptides using size exclusion chromatography. (Sept. Tr. (Grant) 188:11-17.) He has been performing aqueous size exclusion chromatography for over 40 years. (Sept. Tr. (Grant) 188:3-5.)

69. Dr. Grant received a Ph.D. in biochemistry from the University of Wisconsin Madison in 1975. (Sept. Tr. (Grant) 179:13-21.)

70. Dr. Grant edited a book entitled *Synthetic Peptides: A User's Guide* and served as editor of a book series entitled *Techniques of Protein Chemistry*. (Sept. Tr. (Grant) 183:4-12; PTX 760.) In addition, he has authored over 120 peer-reviewed publications. (Sept. Tr. (Grant) 182:24-183:3; PTX 760.)

71. Dr. Grant has served on several editorial boards, including the editorial board for

the *Journal of Biological Chemistry*. (Sept. Tr. (Grant) 184:7-11; PTX 760.) He has also served on several advisory committees for the NIH. (Sept. Tr. (Grant) 184:15-25; PTX 760.)

72. Dr. Grant is the former president of the Association of Biomolecular Resource Facilities, which is an international organization of scientists interested in developing methods for, among other things, determining the molecular weight of polypeptides. (Sept. Tr. (Grant) 183:20-184:6; PTX 760.) He has given many invited lectures in the United States and abroad and has taught graduate level courses in analytical techniques used for proteins and polypeptides, including size exclusion chromatography. (Sept. Tr. (Grant) 185:13-186:4.)

73. Dr. Grant testified regarding the background of the chemistry and molecular weight measurement technique described in the patents-in-suit and Defendants' infringement with regard to the claim limitations relating to molecular weight. Dr. Grant also provided rebuttal testimony regarding the issues of non-obviousness, definiteness, and enablement.

Dr. George Gokel

Sandoz's Response:

Sandoz responds that the entirety of Dr. Gokel's trial testimony, including his cross examinations, should serve as the proper description of his testimony and that any finding regarding his expertise should be based only on the specific subject matter for which the Court accepted Dr. Gokel at trial.

74. Dr. George Gokel is a Distinguished Professor of Science and Associate Director of the Center for Nanoscience at the University of Missouri in St. Louis. (Sept. Tr. (Gokel) 334:3-8; PTX 774.) Dr. Gokel's research laboratory has created hundreds of synthetic peptides. (Sept. Tr. (Gokel) 336:14-16.)

75. Dr. Gokel is an expert in chemistry, including synthetic and peptide chemistry. (Sept. Tr. (Gokel) 340:4-10.)

76. Dr. Gokel received his Ph.D. in chemistry from the University of Southern California in 1971. (Sept. Tr. (Gokel) 334:22-335:4; PTX 774.) He completed a two-year post-doctorate at UCLA under Nobel laureate Donald Cram. (Sept. Tr. (Gokel) 334:22-335:4; PTX 774.)

77. Dr. Gokel has been elected a fellow of the American Association for the Advancement of Sciences, and has received the Izatt-Christensen International Award in macrocyclic chemistry, the American Chemical Society's Midwest Award, and the Chancellor's Award in Research Creativity. (Sept. Tr. (Gokel) 337:2-16; PTX 774.)

78. Dr. Gokel has founded two journals, has served on about a dozen editorial boards, and has refereed dozens of journals. (Sept. Tr. (Gokel) 337:17-22.) He has also published about 450 papers, has written or edited about 10 books, and has given over 350 invited lectures. (Sept.

Tr. (Gokel) 338:4-13.)

79. Dr. Gokel is a named inventor on about 15 patents. (Sept. Tr. (Gokel) 336:23-337:1.)

80. Dr. Gokel testified regarding the chemistry described in the patents-in-suit; Defendants' infringement with regard to the claim limitations relating to copolymer-1 and the process for making copolymer-1; and provided an overall infringement opinion. Dr. Gokel also provided rebuttal testimony regarding the issues of non-obviousness and best mode.

Dr. Nicole Sampson

Sandoz's Response:

Sandoz responds that the entirety of Dr. Sampson's trial testimony, including her cross examinations, should serve as the proper description of her testimony and that any finding regarding her expertise should be based only on the specific subject matter for which the Court accepted Dr. Sampson at trial.

81. Dr. Nicole Sampson is a Professor of Chemistry at Stony Brook University. (Sept. Tr. (Sampson) 536:6-10; PTX 436.) She is an expert in peptide and polymer chemistry. (Sept. Tr. (Sampson) 542:20-25.)

82. Dr. Sampson was awarded a Ph.D. in chemistry from UC Berkeley and did a post-doctoral fellowship at Harvard University. (Sept. Tr. (Sampson) 537:1-11; PTX 436.) She teaches graduate and undergraduate courses in organic reaction mechanisms, physical organic chemistry, and chemical biology. (Sept. Tr. (Sampson) 539:1-7.)

83. Dr. Sampson has authored over 70 peer-reviewed publications, and has been a peer reviewer for many journals, including the *Journal of Organic Chemistry*. (Sept. Tr. (Sampson) 539:17-25.) She has also given over 100 invited lectures at scientific meetings, universities, and corporations. (Sept. Tr. (Sampson) 541:16-20.)

84. Dr. Sampson is a named inventor on three U.S. patent applications, including applications related to methods of preparing polymers and polymer chemistry. (Sept. Tr. (Sampson) 542:4-9; PTX 436.)

85. Dr. Sampson has received several awards for her work in peptide chemistry, including the Pfizer Award in Enzyme Chemistry from the American Chemical Society as well as the American Chemical Society's Cope Scholar Award in Organic Chemistry. (Sept. Tr. (Sampson) 541:21-542:3; PTX 436.)

86. Dr. Sampson testified regarding Defendants' infringement with regard to the copolymer-1 claim limitations under the doctrine of equivalents and provided rebuttal testimony on the issue of non-obviousness.

(2) <u>Mylan's Witnesses</u>

Dr. Walter Owens

87. Dr. Walter Owens is the Vice-President of Global Research and Development at Mylan. (Sept. Tr. (Owens) 594:8-17.) He testified regarding the development of Mylan's generic Copaxone® product, including Mylan's use of universal calibration and testing of its proposed product on the experimental autoimmune encephalomyelitis model.

<u>Sandoz's Response:</u>

This paragraph relates only to the *Mylan* case and requires no response by Sandoz.

Dr. Stephen Kent

88. Dr. Stephen Kent is a professor of chemistry, biochemistry, and molecular biology. (Sept. Tr. (Kent) 648:9-15.) He testified regarding Mylan's best mode defense and provided rebuttal testimony regarding Mylan's infringement with regard to the copolymer-1 claim limitations.

<u>Sandoz's Response:</u>

Sandoz incorporates Mylan's Response to ¶ 88.

Dr. Allen Zeiger

89. Dr. Allen Zeiger is a retired professor of biochemistry and molecular biology at Jefferson Medical College, Thomas Jefferson University. (Sept. Tr. (Zeiger) 785:2-12.) He testified regarding Mylan's obviousness defense.

<u>Sandoz's Response:</u>

Sandoz incorporates Mylan's Response to ¶ 89.

Dr. Susan Rice

90. Dr. Susan Rice has her own consulting firm, Susan A. Rice and Associates, Inc. (Sept. Tr. (Rice) 995:23-996:10.) She testified on behalf of Mylan regarding toxicity data disclosed in the patents-in-suit, and whether the data demonstrate that the claimed copolymer-1 has unexpected results over the prior art.

<u>Sandoz's Response:</u>

Sandoz incorporates Mylan's Response to ¶ 90.

Dr. Ari Green

91. Dr. Ari Green received his M.D. in 2001 from the University of California, San Francisco, where he is now an Assistant Professor of Neurology and the Assistant Director of the Multiple Sclerosis Center. (Sept. Tr. (Green) 1354:16-23; PTX 1964.) He provided testimony on behalf of Mylan regarding secondary considerations of non-obviousness.

Sandoz's Response:

Sandoz incorporates Mylan's Response to ¶ 91.

(3) Sandoz's Witnesses

Dr. John Bishop

92. Dr. John Bishop is Senior Vice President, Pharmaceutical Sciences, at Momenta. (Sept. Tr. (Bishop) 1062:25-1063:5.) He testified regarding the development of Momenta's generic Copaxone® product.

Sandoz's Response:

The Court should make these additional findings regarding Dr. Bishop:

SDZ359. Dr. Bishop received a bachelor's degree in chemistry from Tufts University and a Ph.D. in organic chemistry from the University of California, Berkeley. (Sept. Tr. 1063:17-20 (Bishop).)

SDZ360. Dr. Bishop's responsibilities at Momenta include the chemistry manufacturing and controls section of Momenta's drug development programs. (Sept. Tr. 1063:6-9 (Bishop).) He is also a member of Momenta's executive committee, which manages the company. (Sept. Tr. 1065:9-15 (Bishop).)

Dr. Trevor Laird

93. Dr. Trevor Laird owns Scientific Update, a company that develops training courses and consults for pharmaceutical companies. (Sept. Tr. (Laird) 1112:25-1113:7.) He testified regarding Sandoz's obviousness defense and provided rebuttal testimony on Sandoz's infringement with regard to the "test reaction" claim limitations.

<u>*Sandoz's Response:*</u>

See Sandoz's Opening FFCOL ¶¶ 3-6, which are incorporated by reference.

Dr. Carl Scandella

94. Dr. Carl Scandella is the owner of his own biotechnology consulting firm. (Sept. Tr. (Scandella) 1169:15-18.) He testified on behalf of Sandoz regarding its lack of enablement and indefiniteness defenses.

<u>*Sandoz's Response:*</u>

See Sandoz's Opening FFCOL ¶¶ 40-49, which are incorporated by reference.

Dr. Randolph Wall

95. Dr. Randolph Wall is a professor of microbiology, immunology, and molecular genetics at the UCLA School of Medicine, and Associate Director of the UCLA Broad Stem Cell Center. (Sept. Tr. (Wall) 1747:14-18.) He was a rebuttal witness for Sandoz regarding its lack of enablement and indefiniteness defenses.

<u>*Sandoz's Response:*</u>

See Sandoz's Opening FFCOL ¶¶ 50-53, which are incorporated by reference.

(iii) <u>Witnesses Testifying by Deposition</u>

96. The parties have submitted designated deposition testimony from several witnesses including the following: Weizmann Institute employees Professor Ruth Arnon and Dr. Michael Sela; current or former Teva employees Dr. Irit Pinchasi, Eliezer Konfino, Dr. Alexander Gad and Dr. Haim Varkony; Mylan employees Dr. Stephen Wayne Talton and Dr. Ross Wallingford; Natco employees Dr. Bhujanga Rao, Dr. Duddhi Linga Rao and Dr. Satyanarayana Kota; current or former Momenta employees Dr. Corinne Bauer, Dr. Steve Brugger, Dr. Ganesh Venkataraman and Dr. Mani Iyer; Sandoz employees Dr. Anup Ray and Shrinvasa Rao; and defendants' expert witnesses Dr. Jerard Hurwitz (Mylan) and Dr. Frantisek Svec (Sandoz), who were not called to testify at trial.

II. THE PATENTS-IN-SUIT

97. Each of the Patents-in-Suit is entitled "Copolymer-l improvements in compositions of copolymers." (Stipulations, ¶ 67.) The four inventors named on the patents-in-suit are Eliezer Konfino, Michael Sela, Ruth Arnon, and Dvora Teitelbaum. Eliezer Konfino worked for Teva and retired from the company in December 1991. Michael Sela, Ruth Arnon, and Dvora Teitelbaum worked at the Weizmann Institute. (Stipulations, ¶ 66.)

Sandoz's Response:

The Court should make this additional finding:

SDZ361. The originally named inventors were David Leonov, Ilan Schwarz, Eliezer Konfino, Haim Varkony, Zvi Harel, and Irit Pinchasi. (PTX 11 at TEV000309434.) Drs. Sela, Arnon, and Teitelbaum were substituted as inventors on April 6, 1995 by Kenyon & Kenyon – nearly one year after the original application was filed on May 24, 1994. (PTX 12 at TEV000309530-32.)

98. The Patents-In-Suit each claim priority to (i) U.S. Patent Application No. 08/248,037, filed May 24, 1994 ("the '037 application"), abandoned, and (ii) Patent Application No. 08/344,248, filed November 23, 1994 ("the '248 application"), also abandoned. (Stipulations, ¶¶ 79-80.)

A. The Specification

99. The patents-in-suit are directed to improved compositions of copolymer-1. (PTX 1, col. 1:1-2.) The patents explain that the improved compositions consist of a lower molecular weight form of copolymer-1 that may be used for the treatment of multiple sclerosis. (PTX 1, col. 1: 43-53.)

Sandoz's Response:

If by "lower molecular weight form of copolymer-1," Teva is referring to the requirement that the listed claims must have a weight average molecular weight less than 10 kDa based on Teva's statements throughout the prosecution history distinguishing the '550 patent, Sandoz agrees that the patents explain that the "improved" composition consists of a "lower molecular weight form of copolymer-1." Teva was eventually awarded its patents because it argued in the prosecution history that its invention was distinguishable from the prior art by having a lower molecular weight than the 10 kDa molecular weight of the '550 patent (PTX 26) and a resulting lower toxicity. Without the distinguishing characteristic of having a "lower" molecular weight, the claims are unpatentable because the prior art already included copolymer-1 "that may be used

for the treatment of multiple sclerosis." (E.g., PTX 31 at 413 ("This pilot trial examined the effects of Cop 1 on a selected sample of patients with actively exacerbating multiple sclerosis. . . . The results show that Cop 1, administered subcutaneously for two years at a daily dose of 20 mg, produced clinically important and statistically significant beneficial effects . . . .").)

Without incorporating an implicit reference to the '550 patent's minimum molecular weight of 10 kDa, the statement is incorrect because the asserted claims make no reference to a "lower molecular weight copolymer-1." The cited portions of the specification do not refer to a "lower" average molecular weight or provide a reference point for which the claimed copolymer-1 composition could be described as having a "lower" average molecular weight. The cited portion merely states that the invention relates to copolymer-1 "having an average molecular weight of about 4 to about 8.6 KDa" and "having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa." (PTX 1, '808 patent, col. 1: 43-53.)

100. The patent specification defines the molecular weight characteristics of the lower molecular weight copolymer-1 in several ways. The patent specification explains that the lower molecular weight copolymer-1 can be substantially free of species over 40 kDa, and it describes a preferred composition that has "less than 5% of species" having a molecular weight over 40 kDa. The patents also describe a more preferred composition having "less than 2.5% of species" having a molecular weight over 40 kDa. (PTX 1, col. 1:64–col. 2: 4.)

Sandoz's Response:

If by "lower molecular weight copolymer-1," Teva is referring to the requirement that the listed claims must have a weight average molecular weight less than 10 kDa based on Teva's statements throughout the prosecution history distinguishing the '550 patent, Sandoz agrees with Teva's description of the molecular weight characteristics. Otherwise, the statement is not correct. The specification mentions "copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kDa." (PTX 1, '808 patent, col. 1:43-45.) The prior art

mentioned in the specification – 1971 Teitelbaum (PTX 499) and the '550 patent (PTX 26) – both describe copolymer-1 with average molecular weights less than 40 kDa. The 1971 Teitelbaum reference says nothing about having copolymer-1 species greater than 40 kDa and instead describes two batches of copolymer-1 with weight average molecular weights of 23,100 and 22,800 daltons. (PTX 499 at 243.) The '550 patent describes copolymer-1 with a weight average molecular weight in excess of 10 kDa, and preferably "about 20,000 to 25,000" daltons. (PTX 26, '550 patent, col. 1:57-62, col. 2:19-22.)

101. The patents also describe the claimed lower molecular weight copolymer-1 as "having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa." (PTX 1, col. 2, lines 5-7.) As described further, *infra*, a "molar fraction" in this context refers to the proportion of molecules (as measured by the number of "moles" of molecules) between 2 kDa and 20 kDa, as compared to the total number (or "moles") of all of the molecules in the sample.

Sandoz's Response:

As described in more detail, *infra*, Sandoz disputes this proposed finding to the extent it implies that the claims referring to a percentage of copolymer-1's molar fraction being within a molecular weight range from about 2 kDa to about 20 kDa are not referring to the average molecular weight of a copolymer-1 sample. *See* Sandoz's Response to ¶ 286, which is incorporated by reference.

102. Finally, the lower molecular weight copolymer-1 is defined in the patent by its "average molecular weight." The patent specification provides various ranges for the "average molecular weight" values for the lower molecular weight copolymer-1, and those ranges are reflected in the asserted claims, which are discussed below. As discussed in greater detail in section IV.B., the patents also describe a synthetic process for making the claimed copolymer-1. (PTX 1, col. 4:28–col. 6:3.)

Sandoz's Response:

If by "lower molecular weight copolymer-1," Teva is referring to the requirement that the listed claims must have a weight average molecular weight less than 10 kDa based on Teva's

statements throughout the prosecution history distinguishing the ’550 patent, Sandoz agrees that the lower molecular weight copolymer-1 is defined by its “average molecular weight.”

103. The patent specification describes two ways of producing a lower molecular weight copolymer-1. (PTX 1, col. 2:14-41, col. 2:51–col. 3:18, col. 4:28 – col. 6:3.) First, in Example 1, the patents describe making copolymer-1 and then “fractionating” – or dividing into smaller portions – the resulting copolymer-1 to isolate a low molecular weight fraction. (PTX 1, col. 2:57–col. 3:2.) In addition, the patents provide examples describing processes for making copolymer-1 of varying molecular weights. (PTX 1, col. 4:28-col. 6:3.) Second, the patent describes the use of a particular reagent in the synthetic process—hydrobromic acid in the form of hydrogen bromide (“HBr”) in acetic acid—to cleave an intermediate product called protected copolymer-1 polypeptides into smaller polypeptides. The patent teaches that the time and temperature of the HBr/acetic acid treatment step can be varied to control the amount of cleavage that occurs, and hence, the molecular weight of the resulting copolymer-1. (PTX 1, col. 4:59-col. 6:3.)

Sandoz’s Response:

If by “lower molecular weight copolymer-1,” Teva is referring to the requirement that the listed claims must have a weight average molecular weight less than 10 kDa based on Teva’s statements throughout the prosecution history distinguishing the ’550 patent, Sandoz agrees with Teva’s description of the specification. Otherwise, the methods described in the specification do not call for producing a “lower molecular weight copolymer-1.” For a copolymer-1 to have a “lower” molecular weight, there has to be a reference molecular weight that is higher. The cited passages say nothing about making one batch of copolymer-1 that has a lower molecular weight than another batch. The first method, the “fractionating” method, could be used to fractionate a “higher” molecular weight batch or a “lower” molecular weight batch. It merely divides batches of copolymer-1 into batches of varying sizes. The second method, *e.g.*, the one described in Example 4, can produce copolymer-1 of varying average molecular weights depending on, among other things, how long one lets the reaction run. (PTX 1, ’808 patent, col. 4:63-67 (“The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20º-

28ºC. a test reaction is performed on every batch at different time periods for example, from 10-50 hours.”).)

104. The patent specification describes the use of a calibrated size exclusion chromatography column, Superose 12, to measure the molecular weight distribution and average molecular weight of copolymer-1 samples. (PTX 1, col. 3:6-13.)

Sandoz’s Response:

Sandoz agrees that the two particular batches described in Example 1 were subjected to size exclusion chromatography. None of Examples 2, 3, or 4 mention size exclusion chromatography. Teva’s proposed finding goes too far by claiming that the specification “describes” anything about the size exclusion chromatography. Particularly absent from the “description” is an identification of the standards used to calibrate the Superose 12 column. *See, infra*, for further discussion regarding Teva's failure to enable the patents.

105. Example 2, entitled “Toxicity Analysis,” appears in the specification of each patent-in-suit and describes two different toxicity tests, the *in vivo* mouse test and the *in vitro* RBL degranulation test. (PTX 1, col. 3:21–col. 4:27.) Example 2 describes measuring the toxicity of copolymer-1 using these two tests.

Sandoz’s Response:

Sandoz agrees with the first sentence in TEV105. However, Example 2A does not describe “measuring” degrees of toxicity. A batch is either “toxic” or “non-toxic,” when using the *in vivo* mouse test. (PTX 1, ’808 patent, col. 3:38-42.)

106. Referring to the *in vivo* mouse test, Example 2 states that “[t]hree batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test” in which five mice in each experimental group were injected with the test solution. (PTX 1 at col. 3:23-40.) Example 2 further states that “[if], at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated ‘non-toxic’” and if “one or more of the mice had died or had shown adverse signs, then the batch was designated ‘toxic.’” (PTX 1 at 3:36-40.)

107. Example 2 concludes that “the batches with the average molecular weight of 7.3 and 8.4 KDa were both designated ‘non-toxic’, whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently

designated 'toxic.'" (PTX 1 at 3:41-45.)

108. Example 2 also describes testing in the *in vitro* RBL degranulation test. Example 2 explains that the purpose of the *in vitro* RBL degranulation test was to "screen out those batches of copolymer-1 which invoke substantial degranulation and thus *might* elicit undesirable local and/or systemic side effects." (PTX 1 at col. 3:63-67 (emphasis added).)

109. Example 2 reports that "[f]our batches of copolymer-1, with average molecular weight between 6,250-14,500, were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's" in the *in vitro* RBL degranulation test. (PTX 1 at col. 4:11-15.)

110. Example 2 set forth the results of the *in vitro* RBL degranulation test in the following table:

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,300	<2.5	21.0
13,000	>5	66.9
14,500	>5	67.8

(PTX 1 at col. 4:15-24.)

111. Example 2 concludes with respect to the RBL test data that "[a]s can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin indicative of toxicity is low, and vice versa." (PTX 1 at col. 4:25-27.)

112. The patent specification also describes pharmaceutical compositions comprising the lower molecular weight copolymer-1, as well as the treatment of multiple sclerosis using the same. (PTX 1, col. 1:51-53.)

Sandoz's Response:

While the patent specification states "the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1," Teva's proposed finding goes too far by saying that the specification "describes" the pharmaceutical compositions comprising lower molecular weight copolymer-1 or the treatment of multiple sclerosis. The specification only mentions multiple sclerosis one time after

this passage, stating "copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20 mg." (PTX 1, col. 2:47-48.) That was already known in the prior art from, among other things, the Bornstein paper. (PTX 31 at 413 ("This pilot trial examined the effects of Cop 1 on a selected sample of patients with actively exacerbating multiple sclerosis. . . . The results show that Cop 1, administered subcutaneously for two years at a daily dose of 20 mg, produced clinically important and statistically significant beneficial effects. . . .").)

The specification draws no distinction between "lower" molecular weight copolymer-1 and "higher" molecular weight copolymer-1 in terms of whether either or both can be considered "pharmaceutical compositions." Teva's statement can only be correct if "lower molecular weight copolymer-1" is referring to copolymer-1 with a weight average molecular weight of less than 10 kDa, which was already known in the '550 patent.

B. The Claims

113. Prior to the trial, Plaintiffs voluntarily limited the number of asserted claims to narrow the issues for trial. The asserted claims of the patents-in-suit are claim 1 of the '808 patent; claim 1 of the '589 patent; claims 1, 2 and 3 of the '898 patent; claims 1, 2 and 3 of the '430 patent; claim 1 of the '476 patent; claim 1 of the '161 patent; claims 1 and 6 of the '847 patent; claims 1, 8, 9, 10, 12, 23, 30 and 31 of the '539 patent; and claims 1 and 8 of the '098 patent. Plaintiffs have asserted claim 3 of the '430 patent and claim 3 of the '898 patent against Mylan only.

114. The asserted claims of the patents-in-suit claim, *inter alia,* copolymer-1 with lower molecular weight characteristics, methods of making lower molecular weight copolymer-1, pharmaceutical compositions comprising lower molecular weight copolymer-1, as well as methods of treating multiple sclerosis using the claimed lower molecular weight copolymer-1. The asserted claims contain limitations relating generally to one or more of the molecular weight of the claimed copolymer-1, the process for making the claimed copolymer-1 and the use of the claimed copolymer-1 for treating multiple sclerosis. They are arranged in this manner for further discussion below. (PTX 1-9.)

Sandoz's Response:

Sandoz agrees that the asserted claims must have a molecular weight "lower" than the minimum 10 kDa weight average molecular weight described in the '550 patent.

(i) Molecular Weight Claim Limitations

115. All but three of the 22 asserted claims of the patents-in-suit include numerical limitations directed to molecular weight attributes of either the copolymer-1 end product and/or an intermediate product called trifluoroacetyl copolymer-1. The molecular weight limitations can be categorized as "average molecular weight" and "molar fraction" limitations. (PTX 1-2; PTX 4-9.) In addition, three of the asserted claims are directed to a "predetermined molecular weight profile," and have no numerical limitations. (PTX 3.)

Sandoz's Response:

Sandoz does not dispute Teva's characterization of the claims-in-suit but objects to the extent that Teva implies that what it calls the "molar fraction" limitations do not implicate determination of the average molecular weight of copolymer-1 using size exclusion chromatography. *See infra* for further discussion.

(1) Average Molecular Weight Limitations

116. Claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1 and 6 of the '847 patent and claims 1, 8, 9, 10, 12, 23, 30 and 31 of the '539 patent are directed to copolymer-1 having an "average molecular weight" falling within a particular numeric range. (PTX 1; PTX 2; PTX 7; PTX 8.) For example, claim 1 of the '539 patent provides:

> A copolymer-1 composition comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has ***an average molecular weight of about 4 to about 9 kilodaltons***, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence, and wherein the composition is suitable for treating multiple sclerosis.

(PTX 8, col. 5:18-24.)

Sandoz's Response:

Sandoz agrees with the above, but also notes that claims 1 and 2 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent, also require the measurement of an average

molecular weight because they have a limitation directed to copolymer-1 "within the molecular weight range from about 2 kDa to about 20 kDa." (E.g., PTX 4, '430 patent, claim 1.) While the molecular weight ranges of these claims are expressed in terms of percentages of the "molar fraction," all asserted claims with "molar fraction" or "species" limitations require the use of SEC calibration standards to determine the average molecular weight. (Sept. Tr. 1224:22-1227:4 (Scandella).)

117. The asserted claims containing "average molecular weight" limitations require copolymer-1 having an average molecular weight of "about 5 to 9 kilodaltons" (claim 1 of the '808 patent, claim 1 of the '589 patent), "about 4 to about 9 kilodaltons" (claims 1 and 6 of the '847 patent, claims 1, 8, 9, 12, 23, 30 and 31 of the '539 patent), and "6.25 to 8.4 kilodaltons" (claim 10 of the '539 patent). (PTX 1; PTX 2; PTX 7; PTX 8.)

(2) Molar Fraction Limitations

118. Several of the asserted claims include limitations relating to the molecular weight distribution of a sample of copolymer-1 or the intermediate TFA copolymer-1. These "molar fraction" limitations are expressed as a certain percentage of the copolymer-1 polypeptides (or TFA copolymer-1 molecules) having molecular weights falling within a molecular weight range or above a particular molecular weight value. (PTX 4; PTX 5; PTX 6; PTX 8; PTX 9.)

Sandoz's Response:

All asserted claims with "molar fraction" or "species" limitations require the use of SEC calibration standards to determine the average molecular weight. (Sept. Tr. 1224:22-1227:4 (Scandella).)

119. Claim 1 of the '430 patent exemplifies the copolymer-1 molar fraction and TFA copolymer-1 molar fraction limitations:

> Copolymer-1 having over 75% ***of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa,*** prepared by a process comprising the steps of:
>
> reacting protected copolymer-1 with hydrobromic acid to form ***trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20*** kDa, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and treating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction

> within the molecular weight range from about 2 kDa to about 20 kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa.

(PTX 4, col. 5:21–6:8.)

120. The copolymer-1 "molar fraction" limitations include "over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa" ('430 patent, claims 1-3); "less than 2.5% … over 40 kilodaltons" ('539 patent, claims 8 and 30); "less than 5% … over 40 kilodaltons; and .. over 75% … within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons" ('476 patent, claim 1; '161 patent, claim 1; '098 patent, claim 1); and "less than 2.5% … above 40 kDa" ('539 patent, claims 9, 10 and 31; '098 patent, claim 8). (PTX 4; PTX 5; PTX 6; PTX8; PTX9.)

121. All of the TFA copolymer-1 molar fraction limitations require "trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa" ('430 patent, claims 1-3; '476 patent, claim 1; '161 patent, claim 1). (PTX 4; PTX 5; PTX 6.)

(3) Predetermined Molecular Weight Profile Limitations

122. Claims 1, 2 and 3 of the '898 patent do not include any numerical molecular weight limitations; rather, they require that the copolymer-1 have a "predetermined molecular weight profile." (PTX 3.) As an example, claim 1 of the '898 patent provides:

> A method of manufacturing ***copolymer-1 of a predetermined molecular weight profile***, comprising the steps of: selecting a predetermined molecular weight profile, reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having the predetermined molecular weight profile, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and
> treating said trifiuoroacetyl copolymer-1 having the predetermined molecular weight profile with aqueous piperidine solution to form copolymer-1 having the predetermined molecular weight profile.

(PTX 3, col. 5:35-6:11.)

Sandoz's Response:

Sandoz respectfully disagrees with the Court's construction of the term "predetermined" to the extent it does not incorporate the requirement of a test reaction in each instance for the reasons stated in Sandoz's claim construction papers. Regardless, Teva's only remaining claim

with the word "predetermined" has an express "test reaction" limitation, requiring the determination of both time and temperature with a "test reaction." Because Sandoz's proposed in-process control uses viscosity instead of "time" to determine the stopping point of the reaction, Sandoz does not infringe claims 1, 2, or 3 of the '898 patent. Under that scenario, any error is harmless.

(ii) Process Limitations

123. Twelve of the asserted claims are directed either to a method of manufacturing copolymer-1 having the desired molecular weight characteristics or to copolymer-1 that is made by a particular process. Although the details of each claim may vary, claim 1 of the'589 patent is illustrative of the claims directed to a process for making the claimed copolymer-1:

> Copolymer-1 having a molecular weight of about 5 to 9 kilodaltons, ***made by a process*** comprising the steps of:
>
> reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1, treating said trifluoroacetyl copolymer-1 with aqueous piperidine solution to form copolymer-1, and purifying said copolymer-1, to result in copolymer-1 having a molecular weight of about 5 to 9 kilodaltons.

(PTX 2, col. 6:4-13.)

124. The asserted process for making and product-by-process claims are claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1-3 of the '898 patent, claims 1-3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, and claims 1 and 6 of the '847 patent. Claims 1-3 of the '898 patent; claims 1-3 of the '430 patent; claim 1 of the '476 patent and claim 1 of the '161 patent also require that the HBr treatment step "take[] place for a time and at a temperature predetermined by test reaction." (PTX 3; PTX 4; PTX 5; PTX 6.)

Sandoz's Response:

Sandoz does not dispute any portion of the selective description of these claims, but notes that in addition to claim 1 of the '161 patent, claims 1-3 of the '898 patent, claims 1-3 of the '430 patent, and claim 1 of the '476 patent also require a "time" and "temperature" predetermined by a test reaction. (PTX 3, 4, 5, and 6.) Because Sandoz uses a viscometer to measure viscosity

instead of a clock to measure time in Step 2 of the method claims, Sandoz does not infringe any of those asserted claims.

(iii) Treatment of Multiple Sclerosis

125. Ten of the asserted claims include limitations relating to the treatment of multiple sclerosis. Claim 1 of the '476 patent and claims 23, 30 and 31 of the '539 patent are directed to methods for treating multiple sclerosis. Claim 1 of the '161 is directed to "[a] composition for the treatment of multiple sclerosis." Claims 1 and 8-10 of the '539 patent recite "wherein the composition is suitable for treating multiple sclerosis." Claim 12 of the '539 patent recites "a dose therapeutically effective to treat multiple sclerosis of a copolymer-1 composition." (PTX 5; PTX 6; PTX 8.)

(iv) Pharmaceutical Composition

126. Four of the asserted claims include limitations relating to the use of the lower molecular weight copolymer-1 as a pharmaceutical composition. Claims 12, 23, 30 and 31 of the'539 patent are directed to the use of lower molecular weight copolymer-1 as a pharmaceutical composition. (PTX 8.) For example, claim 12 of the '539 provides:

> A pharmaceutical composition comprising:
>
> a dose therapeutically effective to treat multiple sclerosis of a copolymer-1 composition, wherein the copolymer-1 composition comprises a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence; and a pharmaceutically acceptable excipient.

(PTX 8, col. 5:54-63.)

Sandoz's Response:

If by "lower molecular weight copolymer-1," Teva is referring to the requirement that the listed claims must have a weight average molecular weight less than 10 kDa based on Teva's statements throughout the prosecution history distinguishing the '550 patent, Sandoz has no objection to Teva's characterization of the asserted claims. Otherwise, the statement is incorrect because the asserted claims make no reference to a "lower molecular weight copolymer-1."

III. BACKGROUND ON THE WEIZMANN INSTITUTE'S AND TEVA'S WORK ON COPOLYMER-1

A. Multiple Sclerosis

127. Multiple sclerosis ("MS") is an inflammatory disease of the central nervous system first recognized in the 1860s by the French neurologist Jean-Martin Charcout. (*See* Sept. Tr. (Lisak) 88:8-89:18.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Lisak's testimony at trial.

128. MS is an unpredictable disease involving two of the most complex systems in the body – the immune system and the central nervous system. (Sept. Tr. (Lisak) 136:3-10.) In persons afflicted with MS, autoimmune cells attack myelin, a protective sheath wrapped around nerves found in the brain and the spinal cord. (Sept. Tr. (Lisak) 88:8-89:4.) This leads to the degeneration of myelin and, eventually, the degeneration or death of underlying nerve cells. (Sept. Tr. (Lisak) 90:4-92:11.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Lisak's testimony at trial.

129. This degeneration process eventually prevents the central nervous system from functioning properly as the brain is no longer able to send or receive messages to and from various parts of the body and other functions of the brain or spinal cord are impaired. (Sept. Tr. (Lisak) 90:4-92:11.) The immune system's attack on myelin causes multiple lesions or scars to form on the brain as well as the spinal cord as MS progresses. (Sept. Tr. (Lisak) 89:11-15.) The appearance of these multiple scars or scleroses accounts for the disease name "multiple sclerosis." (Sept. Tr. (Lisak) 89:11-15.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Lisak's testimony at trial.

130. The most common form of MS is Relapsing-Remitting Multiple Sclerosis ("RRMS"). (Sept. Tr. (Lisak) 96:17-19.) Approximately 85% of all MS patients have the Relapsing-Remitting form of the disease. (Sept. Tr. (Lisak) 89:11-15.) Patients with RRMS experience periodic relapses or attacks which are accompanied by steadily worsening disability as the functioning of the nervous system becomes more impaired over time. (Sept. Tr. (Lisak) 95:16-96:25.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Lisak's testimony at trial.

131. The symptoms of RRMS include blurred and double vision, loss of balance and coordination, tremors, fatigue, bladder and bowel dysfunction, paralysis, and even death in some patients. (Sept. Tr. (Lisak) 92:20-93:21.) Patients may exhibit different neurologic symptoms at various times and many patients become permanently disabled. (Sept. Tr. (Lisak) 92:20-93:21.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Lisak's testimony at trial.

132. The initial onset of MS typically occurs early in life - between the ages of 20 and 40. (Sept. Tr. (Lisak) 94:10-18.) As Dr. Robert P. Lisak, a practicing neurologist, testified, the disease thus strikes patients in the "prime of life" - right at the time when they are beginning their careers, finishing school, or beginning to raise a family. (Sept. Tr. (Lisak) 94:10-18.) There is no way to predict when relapses associated with MS will occur and thus the disease acts like a "hanging sword," threatening sufferers with future attacks of unknown length that may result in increased or complete disability. (Sept. Tr. (Lisak) 97:1-9.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Lisak's testimony at trial.

133. Prior to the 1990s, there were no treatments available to prevent relapses or slow the progression of disability associated with MS. (Sept. Tr. (Lisak) 102:2-9; Sept. Tr. (Green) 1391:21-1392:4.) A physician's only option was to treat a patient's symptoms and to try to shorten the duration of a relapse. (Sept. Tr. (Lisak) 102:2-9; Sept. Tr. (Green) 1391:21-1392:4.)

Sandoz's Response:

Teva asserts that there were no "available" treatments to prevent relapses or slow the progression of disability associated with MS, but this is incorrect. Dr. Bornstein's compassionate use trial was available to patients at this time, and his BR-1 trial, in which patients could enroll as early as 1981, had already been concluded and the results published by 1987. (*See* PTX 31; DTX 1303; July Tr. 355:19 – 356:2 (Pinchasi); Sept Tr. 154:10-17, 158:6-10 (Lisak).)

B. Discovery of Copolymer-1 at the Weizmann Institute

134. Professor Ruth Arnon, Professor Michael Sela and Dr. Dvora Teitelbaum are Ph.D. immunologists who worked together at the Weizmann Institute, a world-renowned research institute located in Rehovot, Israel. (July Tr. (Pinchasi) 9:12-20; 16:11-17:5; July Tr. (Arnon) 302:23-303:13, 304:11-17; 304:18-305:14.)

Sandoz's Response:

The term "world-renowned" is so vague as to prevent Sandoz from responding, and on that basis, Sandoz disputes this finding. Moreover, as Dr. Kimber testified, "excellent people can get poor results sometimes. Just because you work at a prestigious institute doesn't guarantee" success. (July Tr. 445:1-15 (Kimber).)

135. In about 1966, Professor Arnon and her colleagues became interested in studying an autoimmune disease called experimental autoimmune encephalomyelitis ("EAE"), which is an animal model for multiple sclerosis. (July Tr. (Arnon) 309:11-310:10.) It was recognized by that time that EAE was induced by a single protein called myelin basic protein ("MBP"), but nothing was known about the mechanism of the disease. (July Tr. (Arnon) 309:11-310:10.) Professor Arnon and her colleagues theorized that if they could produce a synthetic polymer that mimicked MBP, it could be used as a research tool to study the mechanism of EAE. (July Tr. (Arnon) 309:11-311:8.)

Sandoz's Response:

Sandoz does not dispute that this was Professor Arnon's testimony at trial.

136. Professor Arnon and her colleagues synthesized three synthetic polymers, which they called copolymer-1, copolymer-2 and copolymer-3. The copolymers differed in their amino acid composition, but were all targeted to have a molecular weight of 23,000 daltons, which was the molecular weight of MBP. (July Tr. (Arnon) 310:11-311:8.)

Sandoz's Response:

Sandoz does not dispute that this was Professor Arnon's testimony at trial.

137. Professor Arnon and her colleagues tried without success for over a year to use the synthetic copolymers to induce EAE in animals. (July Tr. (Arnon) 310:11-23.) Eventually, it occurred to them that the synthetic copolymers they had made were not similar enough to MBP to induce EAE, but might be similar enough to MBP to compete with it and prevent its activity. (July Tr. (Arnon) 310:11-23.)

Sandoz's Response:

Sandoz does not dispute that this was Professor Arnon's testimony.

138. The experiments they set up to test their hypothesis were successful. (July Tr. (Arnon) 310:11-23.) Instead of inducing EAE, copolymer-1 was very effective in suppressing EAE. (July Tr. (Arnon) 310:24-311:13.) The other two copolymers were much less effective. (July Tr. (Arnon) 311:9-13.)

Sandoz's Response:

Sandoz does not dispute that this was Professor Arnon's testimony.

139. At the time of their discovery that copolymer-1 was effective in suppressing EAE, there were practically no treatments available for multiple sclerosis. (July Tr. (Arnon) 311:14-23.) The only options for patients were immunosuppressive drugs, but these had very severe side effects and were not routinely used. (July Tr. (Arnon) 311:14-23.)

Sandoz's Response:

Teva's assertion that there were "practically no treatments available for multiple sclerosis" is vague and misleading. Moreover, the testimony of Dr. Arnon, an immunologist and biochemist, and not a clinical expert on the treatment of MS, is both improper and irrelevant. Finally, while Sandoz does not dispute that Dr. Arnon testified as to the "very severe side effects" of immunosuppressive drugs, this phrase is so vague as to prevent Sandoz from properly responding, and on that basis, Sandoz disputes this proposed finding.

140. Professor Arnon and her colleagues published their initial findings in 1971 in the European Journal of Immunology ("1971 Teitelbaum article"). (PTX 499.) The article described copolymer-1 as having a molecular weight of 23,000 daltons. (July Tr. (Arnon) 311:24-312:22; PTX 499 at 242.)

Sandoz's Response:

Teva does not dispute that Professor Arnon and her colleagues published their findings, but the statement that the article described copolymer-1 as having a molecular weight of 23,000 daltons is misleading. The article indicates that molecular weight was determined using ultracentrifugation, but there is no explicit description in the article of the *type* of molecular weight referenced. Dr. Scandella testified that, using the analytical technique described in the article, it must be referring to weight average molecular weight. (Sept. Tr. 1290:6-10 (Scandella); 1483:25-1484:4 (Grant).) *See also* Sandoz's Opening FFCOL ¶¶ 171-249.

141. In 1974, the PTO granted U.S. Patent No. 3,849,550 (the '550 Patent") to Yeda. (DTX 1219.) The patent named Professor Arnon, Professor Sela, Dr. Teitelbaum and their co-workers as inventors, and disclosed and claimed the copolymers that they discovered could treat

EAE. (DTX 1219.)

Sandoz's Response:

As Teva admits above, EAE is a model for MS. The '550 patent even states that it was a model for EAE. (DTX 1219, col. 1:29-31.) As such, Drs. Arnon, Sela and Teitlebaum discovered that certain copolymers including copolymer-1, could treat EAE, and therefore, could also be effective in treating MS.

C. The Bornstein Clinical Trial

The first placebo controlled clinical study of copolymer-1 for the treatment of multiple sclerosis was conducted by Professor Murray Bornstein of the Albert Einstein College of Medicine in New York (the "Bornstein trial"). (July Tr. (Arnon) 316:6-15; July Tr. (Pinchasi) 22:4-24; Sept. Tr. (Lisak) 108:25-104:13.) Fifty patients were enrolled in the pilot trial, 25 of whom received copolymer-1. (Sept. Tr. (Lisak) 109:24-110:4; PTX 31 at 408.)

Sandoz's Response:

Teva does not dispute that this was Dr. Lisak's and Dr. Arnon's testimony at trial, or that the Bornstein study was the first placebo-controlled study of copolymer-1. This statement is misleading, however, because several trials, although not placebo-controlled, had been conducted on copolymer-1 prior to the Bornstein trial. (July Tr. 315:16 – 317:15 (Arnon).)

142. Professor Arnon and her colleagues at the Weizmann Institute participated in the basic design of the Bornstein trial and supplied Dr. Bornstein with copolymer-1 for use in the trial. (July Tr. (Arnon) 316:16-21.) The copolymer-1 they supplied was intended to have a molecular weight of 23,000 daltons in order to match the molecular weight of MBP. (July Tr. (Arnon) 316:22-317:11.) The batches, however, actually ranged from 14,000 to 23,000 daltons. (July Tr. (Arnon) 317:12-15; Sept. Tr. (Lisak) 110:11-21; PTX 31 at 408.)

Sandoz's Response:

While the Bornstein article stated that the molecular weight of copolymer-1 used in that study had an average molecular weight between 14,000 and 23,000 daltons, Teva later provided

the FDA with batch-by-batch detailed records showing that the molecular weight of the copolymer-1 used in the Bornstein BR-1 study ranged from 11,000 to 25,200 daltons, as determined by ultracentrifugation. (DTX 1028 at TEV000002330-31 (Table 2 (Batch 320) and Table 3 (Batch 23); DTX 1396 at 59:4-61:20 (Nicholas); DTX 4017 at 127:22-132:11 (Gad).)

143. The results of the Bornstein trial were published in 1987 in the New England Journal of Medicine ("1987 Bornstein article"). (July Tr. (Arnon) 327:22-328:9; Sept. Tr. (Lisak) 108:25-109:13; PTX 31.) While the results from that study were encouraging, they did not definitively establish whether the copolymer-1 composition studied was a safe and effective treatment for RRMS. (PTX 31 at 408; Sept. Tr. (Lisak) 108:25-111:22.)

Sandoz's Response:

Teva's assertion that the Bornstein trial did not "definitively establish" whether copolymer-1 composition studied was a safe and effective treatment for RRMS is so vague as to prevent Sandoz from responding, and on that basis, Sandoz disputes this finding. Moreover, Teva's argument is contradicted by the testimony of Dr. Pinchasi, who characterized the Bornstein trial as one of Teva's two "pivotal" studies, and by Teva's NDA. (July Tr. 272:15-25 (Pinchasi); DTX 1023 at TEV000000453.)

D. Toxicity Testing Of Copolymer-1 By the Weizmann Institute

144. During the Bornstein trial, Dr. Bornstein notified Professor Arnon and her colleagues that some of the patients were experiencing local injection site reactions and that, on rare occasions, some patients experienced systemic side effects that included difficulty breathing, palpitations, severe flush, sweating and severe anxiety. (July Tr. (Arnon) 317:16-320:6; July Tr. (Pinchasi) 23:17-24:23; PTX 28.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Arnon's and Dr. Pinchasi's testimony at trial.

145. Dr. Bornstein's reports of these side effects in his patients were of grave concern to Professor Arnon. (July Tr. (Arnon) 320:7-16.) She knew that copolymer-1 was to be given to patients on a daily basis, so any side effects would be a severe issue. (July Tr. (Arnon) 320:7-16.) At that point, however, she and her colleagues had no idea what was causing the side effects or how they could get rid of them. (July Tr. (Arnon) 320:7-16.)

Sandoz's Response:

Although Sandoz does not dispute that this was Dr. Arnon's testimony at trial, Sandoz finds Dr. Arnon's assertion of "grave concern" about side effects to be vague and misleading. If the side effects observed in the Bornstein trial were truly such a "severe issue," Teva would never have decided to market Copaxone, which continues to cause all of the side effects observed by Dr. Bornstein. (*See* DTX 1074, at 20 (Copaxone Package Insert.); PTX 697.)

Teva states that "at that point" it had no idea how to get rid of the side effects, in order to imply that it was successful in doing so at a later date. But in reality, Teva's alleged "discovery" of a connection between molecular weight and toxicity, and all of its efforts since that time, have been unable to prevent these side effects in patients, as the current Copaxone label attests. (*See* DTX 1074, at 20 (Copaxone Package Insert.); PTX 697.)

146. Based on the reports from Dr. Bornstein, Professor Arnon and her colleagues looked for screening assays that could be used to differentiate between batches that would cause side effects and those that would not. (July Tr. (Arnon) 320:17-25.) They eventually employed the *in vitro* RBL degranulation test. (July Tr. (Arnon) 320:17-25; DTX 3114.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Arnon's testimony at trial.

147. In the RBL degranulation test, RBL cells are preloaded with radiolabeled serotonin and then exposed to copolymer-1. (July Tr. (Arnon) 327:8-21; July Tr. (Baird) 587:3-589:20.) The amount of serotonin released, or degranulated, by the cells is then measured. (July Tr. (Arnon) 327:8-21; July Tr. (Pinchasi) 25:11-26:1; July Tr. (Baird) 587:3-589:20; DTX 3114.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Arnon's, Dr. Pinchasi's, and Dr. Baird's testimony at trial.

148. The RBL test was then (and still is) used as a model for allergic-type reactions, because the degranulation it exhibits in the presence of a stimulant mimics the immune response of human mast cells—a central cell in the allergic immune response system—in responding to allergens or other substances. (July Tr. (Arnon) 321:8-18, 322:21-323:4; July Tr. (Baird) 576:24-577:7, 578:16-582:16, 585:9-21; PTX 522.)

Sandoz's Response:

149. Sandoz does not dispute that this was Dr. Arnon's and Dr. Baird's testimony at trial. Dr. Kimber testified that there is no correlation between RBL degranulation in response to copolymer-1 and side effects in humans. (July Tr. 379:6-14 (Kimber).) Dr. Pinchasi testified that they could not show a "direct correlation between this histamine release [in RBL cells] and the clinical side effects." (July Tr. 112:19-113:2; DTX 1256.)

150. The Weizmann scientists adopted the term "toxicity" to refer to the results of the RBL degranulation test. (July Tr. (Arnon) 327:8-21.) If 30% or more serotonin was released upon exposure to copolymer-1, the batch was designated "toxic" and discarded. (July Tr. (Arnon) 327:8-330:18; PTX 31 at 409.)

Sandoz's Response:

Dr. Pinchasi testified that the RBL cutoff was set at 40% by the Weizmann scientists. (July Tr. 176:21-177:5 (Pinchasi).) Dr. Pinchasi also authored a December 1989 memo in which she comments that "batches that produce > 50% degranulation are also toxic In-Vivo, thus establishing a non-arbitrary and meaningful cut-off criteria." (DTX 999A at TEV001222393-RC.) Sandoz admits, however, that Dr. Pinchasi emphasized a 30% cut-off at trial.

151. The RBL degranulation test was suggested to Professor Arnon by one of her colleagues at the Weizmann Institute who was very experienced with the test. (July Tr. (Arnon) 321:8-18.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Arnon's testimony at trial. However, this statement is unnecessarily vague, as Teva fails to explain that the RBL degranulation test was suggested by Dr. Dvora Teitelbaum, one of the inventors of copolymer-1 and co-author on the 1971 article reporting its discovery. (July Tr. 173:15-174:5 (Pinchasi); PTX 499.)

152. Before making the decision to go forward with the RBL degranulation test, however, Professor Arnon personally read all the literature about the test, including articles by Dr. Reuben Siraganian's group at NIH. (July Tr. (Arnon) 321:8-18, 322:21-323:4; July Tr. (Baird) 576:24-577:7, 578:16-582:16, 585:9-21; PTX 522.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Arnon's and Dr. Baird's testimony at trial

E. Teva's Development of Copolymer-1 with the Weizmann Institute

153. In November 1987, Teva and Yeda, the commercial arm of the Weizmann Institute, entered into an agreement for the development of copolymer-1. (DTX 1232.) Teva's goal was to take the invention made by the Weizmann Institute scientists and translate it into a useful pharmaceutical product that could be given to multiple sclerosis patients. (July Tr. (Pinchasi) 12:10-16.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Pinchasi's testimony at trial. Sandoz disputes, however, that Teva began working on the copolymer-1 project in 1987. As Teva's documents indicate, Teva had been involved in the copolymer-1 project since at least September of 1986. (*See* DTX 3059.)

The copolymer-1 project at Teva was divided into chemical, analytical, pharmaceutical and biological development teams, which were responsible for different aspects of the project. (July Tr. (Pinchasi) 15:4-18.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Pinchasi's testimony at trial.

154. Dr. Irit Pinchasi served as project manager of the copolymer-1 project at Teva, and was responsible for coordinating all development work. (July Tr. (Pinchasi) 11:6-12, 14:12-15:3.)

Sandoz's Response:

Although Teva would like to downplay Dr. Pinchasi's role in the copolymer-1 project, she testified that as a project manager, her duties were to "coordinat[e] all the in-house work with the different professional groups, as well as liaising with all the external experts, whether they are the scientists who originally developed the idea we are trying to develop or commissioned later on, and also of course to represent the R&D vis-a-vis higher management whenever we came to an important decision point when we had to involve them." (July Tr. 10:21-11:5.)

Dr. Pinchasi was in charge of reviewing the patent application for accuracy, and to ensure it was "in line" with what she knew. (July Tr. 205:9-21.) She was also responsible for final approval of the patent application. (July Tr. 213:12-16.)

155. Because Dr. Pinchasi is not a chemist, she had only high-level managerial responsibility for the chemical, analytical and pharmaceutical aspects of the project. (July Tr. (Pinchasi) 15:4-16:3.) She had more substantive input into the biological aspects of the project. (July Tr. (Pinchasi) 14:12-16:3.)

Sandoz's Response:

As discussed above, Dr. Pinchasi had far more responsibility for the chemical development of copolymer-1 than Teva portrays. She testified that, on the copolymer-1 project, she "coordinated the internal work at Teva, which consisted mostly of chemical development, analytical development, and pharmaceutical development." (July Tr. 14:20:22.) Moreover, Teva's assertion that she had "more substantive input" into the biological aspects of the program is so vague as to prevent Sandoz from being able to adequately respond. Sandoz generally disputes Teva's characterization of Dr. Pinchasi's role in the chemical aspects of the copolymer-1 project. *See*, *e.g.*, Sandoz Opening FFCOL ¶¶ 265-312.

156. The biology team consisted of Dr. Pinchasi at Teva and Professor Arnon and Dr. Teitelbaum at the Weizmann Institute. (July Tr. (Pinchasi) 16:4-18.) Dr. Pinchasi met frequently with both Professor Arnon and Dr. Teitelbaum, and worked in Dr. Teitelbaum's lab for several months. (July Tr. (Pinchasi) 16:19-17:5.) Although Professor Arnon was involved at a higher level, she was consulted on all significant decisions. (July Tr. (Pinchasi) 16:19-17:5.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Pinchasi's testimony at trial. However, the assertion that Dr. Arnon was consulted on "all significant decisions" is so vague as to prevent Sandoz from being able to adequately respond. Sandoz disputes the characterization on that basis. Moreover, Teva implies that Dr. Arnon approved significant decisions in order to imply that it was not only Dr. Pinchasi who was responsible for the conflicting information Teva

provided to the FDA and to the PTO, and for the selection of the intentionally deceptive data submitted with the patent application. Importantly, however, Dr. Arnon was not consulted on the night in May 1994 when Dr. Pinchasi decided what data and other information to include in and to exclude from Teva's patent application. *See* Sandoz Opening FFCOL ¶¶ 265-312.

157. When Dr. Pinchasi began working on the project, she understood from the Weizmann Institute scientists that copolymer-1 needed to have a molecular weight in the range of MBP, which was about 20,000 daltons. (July Tr. (Pinchasi) 18:6-19:1, 33:6-20.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Pinchasi's testimony at trial.

158. In fact, in 1974, Professor Arnon and her colleagues had published an abstract in the Israeli Journal of Medical Sciences ("1974 Teitelbaum abstract") that reported that copolymers having the same composition as copolymer-1 but with molecular weights lower than 17,000 or higher than 50,000 daltons proved ineffective for suppression of EAE. (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:4; PTX 509 at 1172-73.)

Sandoz's Response:

This finding contains no information regarding the *type* of molecular weight being discussed, and it is therefore misleading and incomplete. Moreover, it is misleading to the extent it implies that Dr. Pinchasi was not aware that copolymer-1 having a molecular weight less than 17,000 daltons would be effective for suppression of EAE. In fact, by 1987, Dr. Pinchasi knew that batches used in the Bornstein (BR-1) study with molecular weights as low as 14,000 daltons (and in actuality, as low as 11,000 daltons, *see* Sandoz's Response to ¶ 160) were effective.

159. Dr. Pinchasi also learned that the molecular weight of the copolymer-1 used in the Bornstein trial was 14,000 to 23,000 daltons. (July Tr. (Pinchasi) 22:4-21, 33:21-34:5.)

Sandoz's Response:

While the Bornstein article stated that the molecular weight of copolymer-1 used in that study had an average molecular weight between 14,000 and 23,000 daltons, Teva later provided the FDA with batch-by-batch detailed records showing that the molecular weight of the

copolymer-1 used in the Bornstein BR-1 study ranged from 11,000 to 25,200, as determined by ultracentrifugation. (DTX 1028 at TEV000002330-31 (Table 2 (Batch 320) and Table 3 (Batch 23); DTX 1396 at 59:4-61:20 (Nicholas); DTX 4017 at 127:22-132:11 (Gad).)

160. Teva therefore aimed at that time to produce a high molecular weight copolymer-1, in the range of 20,000 daltons. (July Tr. (Pinchasi) 18:6-19:1, 33:6-34:5.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Pinchasi's testimony at trial.

F. The Correlation Between Molecular Weight and Toxicity

161. At the beginning of the copolymer-1 project, Dr. Pinchasi and her team were informed about the local and systemic side effects that Dr. Bornstein had seen in his clinical trial. (July Tr. (Pinchasi) 24:2-23.) They learned that the Weizmann Institute scientists had concluded that these side effects were caused by something "toxic" in the copolymer-1 batches, but that Professor Arnon and her colleagues had no idea what that toxic element was. (July Tr. (Pinchasi) 24:24-25:10.) Dr. Pinchasi and her team also learned that the Weizmann Institute scientists had developed the RBL degranulation test in order to screen batches for "toxicity." (July Tr. (Pinchasi) 25:11-26:18.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Pinchasi's testimony at trial. *See* Sandoz Opening FFCOL ¶¶ 265-312.

162. Solving the toxicity problem was one of the major challenges that the Teva and Weizmann Institute scientists initially faced in developing copolymer-1 into a pharmaceutical product, and much of their development work was focused on this issue. (July Tr. (Pinchasi) 26:19-27:6; July Tr. (Arnon) 331:7-333:6.)

Sandoz's Response:

Teva asserts that "solving the toxicity problem" was one of the major challenges, in order to imply that it actually *did solve* that problem by discovering an alleged correlation between lowered toxicity and lower molecular weight copolymer-1. However, as can be seen by Teva's current label for Copaxone, these same side effects, including injection site reactions and systemic side effects (*see* Teva Proposed Finding No. 145,) still occur, and the so-called

"toxicity problem" has not been solved. (*See* DTX 1074, at 20 (Copaxone Package Insert.); PTX 697.) Moreover, Dr. Pinchasi testified that she knew in May, 1994, and admits that she continued to believe in 2003 and 2004, and at trial, that there was no evidence of any correlation between RBL degranulation levels and side effects in humans. (July Tr. 267:11-268:5.)

163. The Teva and Weizmann Institute scientists studied the literature for clues as to what might be causing the toxicity, and investigated many different possibilities. (July Tr. (Pinchasi) 26:19-27:6.) In the end, the literature did not provide an answer. (July Tr. (Pinchasi) 26:19-27:19.)

Sandoz's Response:

The assertion that Teva and the Weizmann investigated "many different possibilities" is so vague as to prevent Sandoz from adequately responding. On that basis, Sandoz disputes this finding.

164. Finally, the Teva and Weizmann Institute scientists discovered, to their surprise, that toxicity was related to the molecular weight of the product. (July Tr. (Pinchasi) 27:25-28:25.) The higher the average molecular weight of a copolymer-1 batch, the higher the probability that the batch will be toxic. (July Tr. (Pinchasi) 27:25-28:25; July Tr. (Arnon) 332:8-333:6; DTX 3567 (Konfino Dep. Tr. Vol. 1) at 62:24-63:9.)

Sandoz's Response:

Sandoz disputes that Teva "discovered" a clear correlation between higher molecular weight copolymer-1 and higher toxicity. *See generally* Sandoz Opening FFCOL ¶¶ 265-312. Further, as discussed below and in Sandoz Opening FFCOL ¶¶ 281-299, Teva's RBL data refutes its assertion that there is a higher "probability" of non-toxicity at lower molecular weights. Dr. Pinchasi admits that the concept of a probability or trend was nowhere in the patent application. (July Tr. 262:12-20.)

165. In particular, they discovered that there was a narrow molecular weight range between 5,000 and 9,000 daltons in which there is a high probability that a copolymer-1 batch will be both active and non-toxic. (July Tr. (Arnon) 333:7-17; July Tr. (Pinchasi) 34:6-35:5.)

Sandoz's Response:

Teva's RBL data does not support this alleged "discovery." *See* Sandoz Opening FFCOL ¶¶ 281-299. [redacted] The RBL data from the admitted exhibits does not support a difference in toxicity between copolymer-1 having molecular weights between 7,000 and 13,000, let alone show that there is a critical range from 5,000 to 9,000 with a higher probability of being both active and non-toxic.

As discussed above and in Sandoz Opening FFCOL ¶¶ 281-299, the RBL data that was available to Teva in May 1994 did not show a clear correlation between, or even a "probability" of lower toxicity at the molecular weight range of 5,000 to 9,000 daltons. Dr. Pinchasi admits that the concept of a "trend" or "probability" of lower toxicity at lower molecular weights was nowhere in the patent application. (July Tr. 262:12-20.)

Moreover, as Dr. Kimber testified, there is no evidence that batches in this range will be non-toxic in humans. (July Tr. 417:9-17; *see* Sandoz Opening FFCOL ¶¶ 300-302.) Dr. Pinchasi also testified that she knew in May, 1994, and admits that she continued to believe in 2003 and 2004, and at trial, that there was no evidence of any correlation between RBL and side effects in humans. (July Tr. 267:11-268:5.)

Finally, to the extent Teva argues that the level of activity was unexpected at the range of 5,000 to 9,000 daltons, there is no evidence of any testing of activity levels in the patent.

166. Teva initially determined toxicity using the Weizmann Institute's RBL degranulation test. (July Tr. (Pinchasi) 29:1-5.) Teva later added an *in vivo* toxicity test in

which copolymer-1 is injected into mice. (July Tr. (Pinchasi) 29:1-13.)

Sandoz's Response:

Teva's documents make clear that the in vivo test was not just "added," but eventually replaced the RBL test. (DTX 999A at TEV001222392-RC – 396-RC.) The record does not contain any documentary evidence that the RBL test was used after 1992. (July Tr. 412:20-22 (Kimber).)

167. The correlation between molecular weight and toxicity that was discovered by the Teva and Weizmann Institute scientists was very unexpected. (July Tr. (Pinchasi) 32:1-6, 34:19-35:5; July Tr. (Arnon) 333:23-334:2.) There was nothing in the literature that indicated such a correlation. (July Tr. (Pinchasi) 32:1-6.)

Sandoz's Response:

See Sandoz Opening FFCOL ¶¶ 229-234, 241-249.

168. It was also unexpected that copolymer-1 in the range of 5,000 to 9,000 daltons would be both non-toxic and active. The Weizmann Institute and Teva scientists believed that a much higher molecular weight would be needed in order for copolymer-1 to have activity because copolymer-1 was meant to mimic MBP, with a molecular weight in the range of 20,000 daltons, and because testing by the Weizmann Institute had previously shown lower molecular weight copolymer-1 to be ineffective. (July Tr. (Pinchasi) 33:6-34:5, 34:19-35:5; July Tr. (Arnon) 312:23-313:18, 316:25-317:11, 333:18-22.)

Sandoz's Response:

See Sandoz Opening FFCOL ¶¶ 172, 229-234, 241-249.

G. Development of Low Molecular Weight Copolymer-1

169. The discovery of the narrow window between 5,000 and 9,000 daltons that would provide active, non-toxic copolymer-1 product was not a welcome one for Teva, as it presented both regulatory and practical challenges. (July Tr. (Pinchasi) 35:12-18, 38:14-39:4, 42:14-24; PTX 41.)

Sandoz's Response:

Sandoz disputes that any such "discovery" was made, but does not dispute that this was Dr. Pinchasi's testimony at trial.

170. From a regulatory perspective, Teva needed to submit to the FDA two pivotal

studies on copolymer-1 in order to obtain regulatory approval to market the product in the United States. The two pivotal studies are supposed to be performed with exactly the same product, having exactly the same characteristics. (July Tr. (Pinchasi) 35:12-36:20, 37:18-38:4.)

Sandoz's Response:

Teva cites no evidence for its assertion that it needed to submit two pivotal studies to the FDA in order to obtain regulatory approval to market the product in the United States. Moreover, Teva did not present any witness, lay or expert, on regulatory compliance or what Teva was required to submit to the FDA.

171. Teva had planned to rely on the Bornstein trial as one of its two pivotal studies. The Bornstein trial, however, used copolymer-1 having a molecular weight between 14,000 and 23,000 daltons. (July Tr. (Pinchasi) 35:18-21, 37:2-14.) Because of the toxicity issues that had been discovered, Teva knew it would have to perform its second pivotal study with much lower molecular weight copolymer-1. Teva understood that the FDA might not accept the Bornstein trial as one of the two pivotal studies if it switched to the lower molecular weight copolymer-1, and that it might therefore have to perform a second trial before copolymer-1 would be approved. (July Tr. (Pinchasi) 37:15-38:4.)

Sandoz's Response:

Teva fails to cite to any evidence to support its assertions that it planned to rely on the Bornstein trial as one of its two pivotal studies, or that it knew its second study would have to use much lower molecular weight copolymer-1. Moreover, this finding is vague in that it ascribes knowledge to "Teva" in general, and not to any specific person working on the project at this time. Teva also asserted that the molecular weight distribution parameters of the batches used in the Johnson and Bornstein trials showed "comparability" and "close conformity." (DTX 1023 at TEV000000490.) Finally, as discussed above, while the Bornstein article stated that the molecular weight of copolymer-1 used in that study had an average molecular weight between 14,000 and 23,000 daltons, Teva later provided the FDA with batch-by-batch detailed records showing that the molecular weight of the copolymer-1 used in the Bornstein BR-1 study ranged from 11,000 to 25,200, as determined by ultracentrifugation. (DTX 1028 at TEV000002330-31

(Table 2 (Batch 320) and Table 3 (Batch 23); DTX 1396 at 59:4-61:20 (Nicholas); DTX 4017 Tr. at 127:22-132:11 (Gad).)

172. From a practical perspective, Teva understood that it would be a challenge to reproducibly produce copolymer-1 having a molecular weight of 5,000 to 9,000 daltons, because the Teva and Weizmann Institute scientists had not yet developed a manufacturing process that could sufficiently control the molecular weight of the final product. (July Tr. (Pinchasi) 38:14-39:4.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Pinchasi's testimony at trial.

173. Notwithstanding these significant challenges, Teva decided that it could not market a product that had a chance of being toxic, so it targeted a molecular weight for copolymer-1 of about 7,000 daltons. (July Tr. (Pinchasi) 38:5-39:4, 81:13-82:19; PTX 708 at TEV000324552.)

Sandoz's Response:

Teva's concern about marketing a product with "a chance" of being "toxic" is misleading, as Teva's current Copaxone product makes clear that side effects continue to occur, regardless of Teva's targeted molecular weight. (*See* DTX 1074, at 20 (Copaxone Package Insert.); PTX 697.)

174. Teva's second pivotal trial began in October 1991. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597 at 1271.) This clinical trial, named the Johnson Study after principal investigator Kenneth Johnson, was a Phase III large-scale, multicenter, placebo-controlled, double-blinded study. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597 at 1268.) A total of 251 patients participated in the two-year trial. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Lisak's testimony at trial.

175. The Johnson Study demonstrated for the first time that copolymer-1 was a safe and effective treatment for patients with RRMS. (Sept. Tr. (Lisak) 110:22-111:22.) The Johnson trial demonstrated, *inter alia*, that daily injections of copolymer-1 resulted in a statistically significant reduction in relapse rates for patients with RRMS. (Sept. Tr. (Lisak) 107:25-108:4; PTX 597 at 1268.) The study concluded in 1994 and the results were published in 1995 in the Journal of Neurology. (PTX 597.)

Sandoz's Response:

Teva's assertion that the Johnson trial was the first time copolymer-1 was demonstrated to be a safe and effective treatment for MS is contradicted by its own documents. As Teva told the FDA in its NDA: "[c]omparability of the drug substance manufactured at the Weizmann Institute and Bio-Yeda and that manufactured at TEVA Plantex is also supported by the consistent clinical efficacy and safety results observed in the two pivotal clinical trials, BR-1 and 01-9001." (PTX 81 at TEV000002341.) Thus, Teva represented to the FDA that prior to the Johnson trial, the Bornstein (BR-1) trial demonstrated the clinical efficacy and safety of copolymer-1.

176. On June 14, 1995, Teva submitted its NDA, relying on both the 1987 Bornstein trial and the Johnson Study to demonstrate the safety and efficacy of copolymer-1. (PTX 81 at TEV000002326.) While Teva represented to the FDA that the safety of the copolymer-1 compositions studied in the Johnson Study and the Bornstein trial were comparable, Teva did not draw any comparisons between the tolerability of the compositions or their propensity to cause injection site reactions. (PTX 881 (Green Dep.) at 111:11-18; PTX 81.)

Sandoz's Response:

Teva argued in its Proposed Finding No. 176 that the Johnson study was the first time copolymer-1 was demonstrated to be a safe and effective treatment, and then admits here that it told the FDA the safety of the copolymer-1 compositions in the Bornstein and Johnson studies were comparable. Dr. Pinchasi also admitted that Teva purposely employed a strategy of trying to convince the FDA that the higher molecular weight copolymer-1 Teva had used in its BR-1 clinical trial was comparable to the lower molecular weight copolymer-1 used in the Johnson clinical trial. (July Tr. 269:3-6, 270:2-6.)

177. Although Teva's NDA set an average molecular weight specification of 4,700 to 13,000 daltons, Teva actually targeted an average molecular weight of 7,000±1,000 daltons for the batches of copolymer-1 that were to be marketed. (July Tr. (Pinchasi) 85:23-89:22.) Teva informed the FDA of this 7,000±1,000 daltons average molecular weight target as part of its NDA submission. (July Tr. (Pinchasi) 85:23-89:22; DTX 1023 at TEV000000455; *see also* July Tr. (Pinchasi) 81:23-85:13; PTX 723 at TEV000599260.)

Sandoz's Response:

Sandoz does not dispute Teva's molecular weight "target," but asserts that it is irrelevant, since Teva told the FDA that it believed the appropriate range for copolymer-1 was 4,700 to 13,000 daltons.

178. Teva set the formal specification at 4,700 to 13,000 daltons originally to maintain a larger margin for average molecular weight in light of potential manufacturing changes that might be necessary to market the product. (July Tr. (Pinchasi) 86:4-86:24.) Batches within the 4,700 to 13,000 daltons specification were still tested for toxicity on the RBL screen and *in-vivo* mouse test and rejected if they failed on either of those screens. (July Tr. (Pinchasi) 86:4-24.)

Sandoz's Response:

Teva argues that it had determined the optimal range for its copolymer-1 product, but admits that it continues to screen batches between 4,700 to 13,000 daltons. This is clear evidence that Teva did not believe a molecular weight between 5,000 and 9,000 daltons was truly determinative of toxicity. If it did, Teva would not bother to continue screening batches within this range. Moreover, Teva has presented no documentary evidence that batches of copolymer-1 were screened using the RBL test after 1992. (*See* PTX 62.)

H. Teva's Later Work on TV-5010

179. The discovery by the Teva and Weizmann Institute scientists that toxicity was correlated with molecular weight was confirmed years later in connection with Teva's TV-5010 project.

Sandoz's Response:

Teva fails to cite any evidence for its assertion that it later confirmed its alleged "discovery" of a correlation between molecular weight and toxicity. In the absence of any evidence, the Court should not accept Teva's bare attorney argument. Moreover, Teva's experience with TV-5010 is irrelevant, because it did not have molecular weights below 13,000 daltons. (July Tr. 279:24 – 280:3.).

180. Years after Copaxone® was introduced to the market, Teva contemplated

developing a high molecular weight copolymer-1 that would be administered as a once-weekly injection. The internal Teva name for this high molecular weight copolymer-1 was TV-5010. (July Tr. (Pinchasi) 104:21-105:6.)

Sandoz's Response:

Teva fails to cite any evidence for what Teva "contemplated" years after Copaxone was introduced. Moreover, "years after" is insolubly vague and prevents Sandoz from being able to adequately respond to this finding. This finding is also vague in that it refers to "high molecular weight copolymer-1" without indicating any particular molecular weight. Without any indication of the definition of "high molecular weight," the TV-5010 study is both misleading and irrelevant. Moreover, Teva's experience with TV-5010 is irrelevant, because it did not have molecular weights below 13,000 daltons. (July Tr. 279:24 – 280:3.)

181. Teva's hypothesis at the time was that if you gave the high molecular weight copolymer-1 to patients on a once-weekly basis, rather than on a daily basis as Copaxone® is administered, it could compensate for the toxicity issues. (July Tr. (Pinchasi) 105:14-24.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Pinchasi's testimony. However, this finding is misleading and vague in that it ascribes a hypothesis to "Teva" generally, and not to any specific witness or Teva employee. Moreover, without any indication of the definition of "high molecular weight," the TV-5010 study is both misleading and irrelevant. Finally, Teva's experience with TV-5010 is irrelevant, because it did not have molecular weights below 13,000 daltons. (July Tr. 279:24 – 280:3.)

182. Teva was never able to put the high molecular weight TV-5010 on the market, however, because severe safety issues were discovered during toxicology studies in animals, which included mortality, severe injection site lesions and systemic effects. (July Tr. (Pinchasi) 105:25-111:9; PTX 158.)

Sandoz's Response:

This finding is vague in that it refers to "high molecular weight" copolymer-1 without indicating any particular molecular weight range or measurement. Without any indication of the definition of "high molecular weight" or the method used to measure that molecular weight, the TV-5010 study is both misleading and irrelevant. Finally, Teva's experience with TV-5010 is irrelevant, because it did not have molecular weights below 13,000 daltons. (July Tr. 279:24 – 280:3.)

I. Lower MolecularWeight Copolymer-1

183. Teva was able to reproducibly achieve the narrow molecular weight range of about 7,000 daltons because of a discovery made by Teva chemist Eliezer Konfino.

Sandoz's Response:

[redacted] Teva refused to bring him to trial. Instead of hearing about Teva's purported discovery from Mr. Konfino, Teva instead used Dr. Pinchasi to interpret what Konfino allegedly discovered. The only Konfino document cited in this section, PTX 36, is just a series of data tables and charts. (PTX 36.) It is dated May 4, 1988, which is six years before Teva sought a patent on the purported discovery.

Regarding Mr. Konfino's "unexpected discovery" of using HBr to cleave the polypeptide bonds, there is clear and convincing evidence in the record that there was nothing new or unexpected. (*E.g.*, Sept. Tr. 1138:16-22, 1139:10-21, 1140:9-1141:16, 1143:1-1144:11, 1147:7-1148:9 (Laird).) In fact, in 1988, one of Teva's outside consultants sent Haim Varkony (an originally named inventor of the patents-in-suit) a letter forwarding a 1965 textbook explaining that HBr can be used to cleave peptide bonds. (PTX 11 at TEV000309434 (Varkony is an original inventor); DTX 1269 at TEV001090146, 181.) The article states that "peptide bonds are

also in danger of being cleaved" when HBr is used (id. at TEV001090182), and has a handwritten circle around the words "tendency to cleavage" in a chart describing the use of HBr to cleave peptide bonds. (*Id.* at TEV001090184; see also Sept. Tr. 1670:21-1673:7 (Sampson).) There are no documents in the record suggesting that Konfino considered the use of HBr to cleave peptide bonds to be novel or advantageous before Teva's consulants shared the 1965 textbook with Teva.

184. When Tqeva scientists began working on the copolymer-1 project, they found that the same starting materials and what they believed to be the same reaction conditions produced copolymer-1 of varying molecular weights. (July Tr. (Pinchasi) 38:14-39:4.)

Sandoz's Response:

See Sandoz Opening FFCOL ¶ 191, Sandoz's Response to ¶ 57. Sandoz also incorporates by reference Mylan's Proposed Findings of Fact and Conclusions of Law Regarding Obviousness, and Mylan's Opposition to Teva's Proposed Findings of Fact and Conclusions of Law Nos. 184-186.

185. Mr. Konfino made the unexpected discovery that the second step of the process for making copolymer-1, which involves the addition of HBr/acetic acid, cleaves, or cuts up, the polypeptide copolymer-1 chains, and therefore lowers the average molecular weight of the product. (July Tr. (Pinchasi) 68:5-25, 76:13-77:18, 81:23-85:13; PTX 36; PTX 36-T; PTX 42.)

Sandoz's Response:

Sandoz disputes that Mr. Konfino made any such "discovery." Indeed, Dr. Trevor Laird testified that it was well known at the time of the invention to use HBr in acetic acid to cleave peptide bonds. (Sept. Tr. 1138:16-22, 1139:10-21, 1140:9-1141:16, 1143:1-1144:11, 1147:7-1148:9.) Teva's expert Dr. Sampson also agreed that multiple publications available prior to 1994 would have allowed a person of skill in the art to conclude that use of HBr in acetic acid resulted in peptide bond cleavage. (Sept. Tr. 1663:25-1664:10, 1666:12-19 (referring to DTX

3329), 1666:20-1667:21, (referring to DTX 3327), 1668:19-1669:9 (referring to DTX 1781), 1670:2-20 (referring to DTX 1783).)

Sandoz also incorporates by reference Mylan's Proposed Findings of Fact and Conclusions of Law Regarding Obviousness, and Mylan's Opposition to Teva's Proposed Findings of Fact and Conclusions of Law Nos. 184-186.

186. Mr. Konfino found that he could control the average molecular weight of the final copolymer-1 product by controlling the time and temperature of the second step of the process. The longer the reaction is run, and the higher the temperature, the more cleavage occurs and the lower the average molecular weight of the product. (July Tr. (Pinchasi) 68:5-25, 76:13-77:18, 81:23-85:13; PTX 36; PTX 36-T; PTX 42.)

Sandoz's Response:

See Sandoz Opening FFCOL ¶ 191, Sandoz's Response to ¶ 57.

187. Mr. Konfino also discovered that the time and temperature for the Step 2 reaction that would provide copolymer-1 of approximately 7,000 daltons could be determined by running a test reaction. (July Tr. (Pinchasi) 81:23-82:19.)

Sandoz's Response:

188. Sandoz does not dispute that this was Dr. Pinchasi's testimony at trial. This "test reaction," according to Dr. Pinchasi, involved taking the copolymer-1 produced after Step 1, and "subjecting a small amount of it to HBr in glacial acetic acid from a specific source that we planned to use later in the final production scale, and adjusting exactly, finding exactly what is the time needed for reaction, where you keep the temperature fixed." (July Tr. 81:25-82:19 (Pinchasi).) Once Dr. Pinchasi determined the appropriate time and temperature for that small scale batch, the process would be "repeated exactly under the same conditions … with an entire batch to be produced," *i.e.*, the process was reproduced "on a much larger scale." (July Tr. 82:13-17.) Sandoz also disputes that this kind of test reaction was novel, and that Mr. Konfino "discovered" it, since as Dr. Laird testified, these kinds of test reactions were already well known in the art by 1994. (Sept. Tr. 1116:6-8 (Laird).)

IV. BACKGROUND ON POLYPEPTIDE CHEMISTRY, SYNTHESIS AND ANALYTICAL TESTING

A. Polypeptide Chemistry

189. A polymer is a molecule composed of smaller subparts called monomers. (Sept. Tr. (Grant) 191:9-16; PTX 986 at 4.) A copolymer is a polymer composed of more than one type of monomer. (Sept. Tr. (Grant) 191:19-192:1; PTX 986 at 4.)

Sandoz's Response:

Undisputed.

190. The monomers that make up copolymer-1 are amino acids. (Sept. Tr. (Grant) 192:2-3.) An amino acid is a molecule that contains an amino group, a carboxylic acid group, and a side chain. (Sept. Tr. (Grant) 192:4-19; Sept. Tr. (Gokel) 341:6-25; PTX 986 at 5; PTX 987 at 4.)

Sandoz's Response:

Undisputed.

191. A polypeptide is a molecule made up of amino acid monomers that are joined together by peptide bonds. (Sept. Tr. (Grant) 180:17-21; Sept. Tr. (Gokel) 344:11-22.) Copolymer-1 is a mixture of polypeptides. (PTX 1, col. 1:32.)

Sandoz's Response:

Undisputed.

192. The polypeptides comprising copolymer-1 are synthetic – meaning that they are made in a laboratory – and they are composed of four amino acids: glutamic acid, lysine, alanine, and tyrosine. (Sept. Tr. (Grant) 180:22-23, 183:13-19, 192:20-193:23; Sept. Tr. (Gokel) 342:12-344:10, 344:23-345:12; PTX 986 at 6-7; PTX 987 at 6, 8-11.)

Sandoz's Response:

Undisputed.

193. The individual polypeptide molecules, or "species," in copolymer-1 have different lengths and sequences. For that reason, the molecular weight of a sample of copolymer-1 can best be described either as an average molecular weight or as a molecular weight distribution. (Sept. Tr. (Grant) 194:14-195:2, 195:7-10, 1544:23-1545:11; Sept. Tr. (Scandella) 1193:24-1194:2; PTX 986 at 8.)

Sandoz's Response:

Undisputed. The estimated molecular weight of copolymer-1 "has to be treated as an average molecular weight," because even the smallest sample that can be analyzed contains billions of molecules with different individual molecular weights. (Sept. Tr. 1193:24-1194:11; 1225:18-1226:1 (Scandella).) *See* Sandoz's Response to ¶ 451, which is incorporated by reference.

194. The molecular weight of an individual polypeptide molecule is the sum of the atomic weights of the atoms comprising the molecule. (Sept. Tr. (Grant) 193:24-194:13.) A molecular weight distribution, by contrast, is a description of the molecular weights of the polypeptides that make up a mixture of polypeptide molecules. (Sept. Tr. (Grant) 198:9-13.)

Sandoz's Response:

Although the sum of the atomic weights is a textbook definition of molecular weight, that definition is not useful for copolymer-1. Due to the complexity of copolymer-1, its molecular weight must be estimated in the laboratory. (Sept. Tr. 1191:23-1192:9 (Scandella).) As Dr. Scandella testified, "for a large complicated molecule like cop-1, the meaning of molecular weight becomes fuzzy. One has to specify what method one is going to use to measure molecular weight, because different methods will give you a different answer." (Sept. Tr. 1193:7-10 (Scandella).) Dr. Wall agreed: "For something that's as complicated as copolymer-1 with millions or billions of who knows how many different species, molecular weight becomes much more of an experimental definition and the ways in which you find that molecular weight really depends on the experimental technique that you use." (Sept. Tr. 1762:7-12 (Wall).) Dr. Wall further testified that copolymer-1 "is an incredibly complicated molecule, probably one of the most complicated mixtures that's ever been analyzed -- certainly that I know of. And it is that immense diversity of molecules and structures and sequences and mixture that in fact confounds the ability of even very sophisticated investigators to arrive at a molecular weight." (Sept. Tr. 1812:17-22 (Wall).) Teva explained the complexity of copolymer-1 to the FDA:

> Because the glatiramer acetate in Copaxone® is not a single molecular entity, but rather a heterogenous polypeptide mixture that contains a huge, perhaps incalculable number of active amino acid sequences ('epitopes') in a defined range of molar ratios, FDA has long recognized that 'Copolymer-1 [Copaxone®] is not a conventional drug, either in chemical composition or in its presumed mechanism of action.'

(DTX 1738 at KRULL0000024-25.)

B. Synthesis of Copolymer-1

195. The varying lengths and sequences of the polypeptide chains in a sample of copolymer-1 are a result of the method of its synthesis. (Sept. Tr. (Grant) 195:11-197:10.)

Sandoz's Response:

Undisputed.

196. The patents-in-suit teach that copolymer-1 is synthesized using a four-step process in a "batch" method of synthesis. (Sept. Tr. (Gokel) 352:2-354:15; Sept. Tr. (Grant) 1401:19-1402:4; PTX 1, col. 4:30-col. 6:3; PTX 987 at 22.)

Sandoz's Response:

Undisputed.

197. In Step 1, the N-carboxyanhydrides, or activated versions, of the amino acids glutamic acid, lysine, alanine, and tyrosine are combined in the presence of a chemical called an initiator. The initiator starts the reaction of the amino acids by joining with one of the activated amino acids, which removes the N-carboxyanhydride group and allows the first amino acid to join to a second amino acid, which in turn allows the second amino acid to react with a third amino acid, and so forth. Each initiator molecule starts a new polypeptide chain. This sequence of reactions results in polymerization of the amino acids into polypeptide chains. (Sept. Tr. (Grant) 195:17-197:16; Sept. Tr. (Gokel) 349:3; PTX 986 at 9; PTX 987 at 14.)

Sandoz's Response:

Undisputed.

198. Glutamic acid and lysine each have two sites that can form bonds with other amino acids. In order to ensure that the amino acids combine with each other in a straight chain and do not become branched during the polymerization step, protecting groups are used to block the reactive sites on the side chain of each of these amino acids. Benzyl groups are used to protect the glutamic acid and TFA groups are used to protect the lysine. (Sept. Tr. (Gokel) 342:16-343:23, 345:5-346:25; PTX 987 at 7, 12-13.)

Sandoz's Response:

Undisputed.

199. The result of the Step 1 polymerization is called "protected copolymer-1" because the side chains of glutamic acid and lysine are protected by the benzyl and TFA protecting groups, respectively. Protected copolymer-1 is a mixture of polypeptides that have different lengths and amino acid sequences. (Sept. Tr. (Grant) 195:17-197:16; Sept. Tr. (Gokel) 347:1-349:8, 353:4-16; PTX 987 at 15, 22.)

Sandoz's Response:

Undisputed.

200. In Step 2, the protected copolymer-1 is treated with HBr/acetic acid to remove the benzyl protecting groups from glutamic acids (deprotection). During this deprotection process, the polypeptide chains are also cleaved (depolymerized), which results in shorter polypeptide chains. (Sept. Tr. (Gokel) 347:1-350:5, 353:17-25; PTX 987 at 16-18, 22.) The resulting product of the Step 2 (deprotection/depolymerization) is called TFA copolymer-1 because the TFA protecting groups remain on the lysine residues. (Sept. Tr. (Gokel) 350:11-18.)

Sandoz's Response:

Undisputed.

201. The time and temperature of the HBr/acetic acid reaction of Step 2 determines the extent of cleavage of the polypeptide chains and the resulting average molecular weight of the copolymer-1 product. (PTX 1, col. 4:59-65.) The longer the reaction is run or the higher the temperature, the more cleavage occurs and the lower the average molecular weight of the product. This step is therefore used to control the molecular weight of the resulting copolymer-1. (Sept. Tr. (Sampson) 1641:6-1642:8; PTX 992 at 6-7; July Tr. (Pinchasi) 81:23-82:19; DTX 1023 at TEV000000455.)

Sandoz's Response:

Relying on the time and temperature of the HBr/acetic acid reaction is not the only mechanism of controlling the molecular weight of the resulting copolymer-1, and indeed, Sandoz and Momenta do not use that mechanism. (*See* Sandoz's Opening FFCOL ¶¶ 1-13.)

202. In Step 3 of the synthetic process, the TFA copolymer-1 is treated with piperidine to remove the TFA protecting groups from the lysines, resulting in copolymer-1. (Sept. Tr. (Gokel) 350:19-22, 351:3-12, 354:1-9; PTX 987 at 15, 22.) The chain lengths of the polypeptides are not affected in the TFA deprotection step. (Sept. Tr. (Gokel) 350:23-351:2.)

Sandoz's Response:

Undisputed.

203. In Step 4 of the synthetic process, the copolymer-1 can be purified by dialysis. In one method of dialysis, acetic acid is used. (Sept. Tr. (Gokel) 350:23-351:2; PTX 1, col. 5:12-col. 6:2; PTX 987 at 22.)

Sandoz's Response:

Undisputed.

C. Size Exclusion Chromatography

204. The patents-in-suit explicitly identify size exclusion chromatography ("SEC") as the method to be used for determining the molecular weight of copolymer-1. (Sept. Tr. (Grant) 186:16-20, 197:17-25, 326:15-18; Sept. Tr. (Scandella) 1227:5-10; PTX 1, col. 3:6-7.)

Sandoz's Response:

Undisputed.

Sandoz agrees that the two particular batches described in Example 1 of the patents were subjected to size exclusion chromatography. None of Examples 2, 3, or 4 mention size exclusion chromatography.

205. SEC, otherwise known as "gel filtration" or "gel permeation chromatography," is a separation and analytical technique that separates molecules based upon their size in solution. SEC can be used to determine the molecular weights of samples, such as polypeptides, as well as their molecular weight distributions. (Sept. Tr. (Grant) 186:5-15, 186:21-187:4, 198:1-3, 198:14-20, 329:14-20, 1411:2-5, 1415:8-17; PTX 553 at 63, last line-64, line 4; PTX 566 at 2, lines 5-7.)

Sandoz's Response:

SEC cannot be used to determine molecular weight directly, because "[b]y itself, a size exclusion chromatography column has no ability to measure molecular weight." (Sept. Tr. 1221:9-10 (Scandella).) Instead, following the SEC run, the molecular weights of the separated material can be estimated with an online detector, such as a light scattering detector, or through the use of a calibration curve. (Sept. Tr. 1211:25-1212:17 (Scandella); DTX 3581 at 7.)

206. SEC was first described in the literature in the late 1950s or early 1960s, and the first commercial SEC instrument was marketed in 1964. (Sept. Tr. (Grant) 1409:17-19; PTX 553 at 63-64; PTX 514 at 199.)

Sandoz's Response:

Undisputed.

207. By 1994 there was a huge volume of scientific literature describing the use of SEC. (Sept. Tr. (Grant) 1409:17-23; Sept. Tr. (Scandella) 1314:15-25.) This literature included textbooks, individual book chapters, and numerous scientific articles. (Sept. Tr. (Grant) 1409:24-1410:2.) For example, N.C. Billingham, Molar Mass Measurements in Polymer

Science (John Wiley & Sons 1977) ("Billingham 1977"), contains a chapter entitled "Gel Permeation Chromatography," which states that "[t]he idea of producing separation of discrete molecular species on the basis of differences in molecular size has been familiar to the biochemist for many years." (PTX 514 at 199.)

Sandoz's Response:

None of the SEC literature in 1994 taught how to determine the molecular weight of a mixture as complex as copolymer-1. (*See, e.g.*, Sept. Tr. 1812:17-22; 1820:25-1821:19 (Wall).) *See* Sandoz's Responses to ¶¶ 194, 209, 451, 466, 475, 489, and 497, which are incorporated by reference.

208. Polypeptides were some of the first substances studied by SEC, and by 1994, the prior art with respect to using SEC to determine the molecular weight of polypeptides was extensive. (Sept. Tr. (Grant) 1410:3-9.)

Sandoz's Response:

None of the SEC literature in 1994 taught how to determine the molecular weight of a mixture as complex as copolymer-1. (*See, e.g.*, Sept. Tr. 1812:17-22; 1820:25-1821:19 (Wall).) *See* Sandoz's Responses to ¶¶ 194, 209, 451, 466, 475, 489, and 497, which are incorporated by reference.

209. By 1994, all aspects of the SEC process—including its theory and practice, and the interpretation of results—had been described in numerous book chapters such as Billingham 1977, the "Gel Filtration" chapter in Protein Purification – Principles, High Resolution Methods and Applications (Jan-Christer Janson and Lars Ryden eds., 1989) ("Janson 1989"), and the "Characterization of Complex Polymers by Size Exclusion Chromatography and High-Performance Liquid Chromatography" chapter from Modern Methods of Polymer Characterization (Howard G. Barth and Jimmy W. Mays, 1991) ("Barth 1991"). (Sept. Tr. (Grant) 1410:10-1412:5, 1414:8-21, 1418:19-1419:21; PTX 514; PTX 553; PTX 566.)

Sandoz's Response:

To the extent "all aspects of the SEC process" includes determining the molecular weight of a mixture as complex as copolymer-1, the SEC literature in 1994 did not describe "all aspects" of the process. (*See, e.g.*, Sept. Tr. 1812:17-22; 1820:25-1821:19 (Wall).) As Teva explained to the FDA in 2008:

> Given the complexity of the glatiramer acetate in Copaxone®....Teva has spent decades studying the correlations among Copaxone®'s chemical, immunological, and biological properties. These studies have led Teva to design and implement a series of well-controlled manufacturing processes and rigorous testing procedures—developed specifically for glatiramer acetate analysis—to ensure the batch-to-batch consistency, safety, and efficacy of the glatiramer acetate in Copaxone®.

(DTX 1738 at KRULL0000030.) Teva also told the FDA that "Teva has developed a unique method of measuring MW distribution based on the separation of glatiramer acetate polypeptides, and calculates the product's MW distribution using a calibration curve generated from a set of well-characterized proprietary polypeptide markers." (DTX 1738 at KRULL0000041; Sept. Tr. 1815:1-1816:4 (Wall).) The asserted patents do not disclose Teva's "unique method of measuring MW distribution," or the use of Teva's "well-characterized proprietary polypeptide markers," which were not even available in 1994. (Sept. Tr. 1816:5-20 (Wall); Sept. Tr. 1281:9-14 (Scandella); Sept. Tr. 1525:6-11 (Grant); PTX 1.) Accordingly, one of ordinary skill in the art would not have been able to use those markers for column calibration in 1994. (Sept. Tr. 1281:9-14 (Scandella); Sept. Tr. 1816:5-20 (Wall).) Teva explained why using exactly the same process is so essential: "[E]ven the most minor changes in the manufacturing of glatiramer acetate-and in the molecular weight distribution of the resulting product-will produce a new molecular entity ('NME') with a significantly different potency and safety and efficacy profile." (DTX 1738 at KRULL0000034.) *See* Sandoz's Responses to ¶¶ 194, 451, 466, 475, 489, and 497, which are incorporated by reference.

210. SEC was in 1994—and still is—the best way of determining the molecular weight distribution of a mixture of polypeptides like copolymer-1. For example, Barth 1991 describes SEC as "a well-recognized technique for the determination of polymer molecular weight distributions." (PTX 566 at 2.) In addition, Billingham 1977 explains that SEC is "used as a matter of routine in very many polymer laboratories" to characterize the molecular weight of polydisperse polymers. (Sept. Tr. (Grant) 198:14-20, 329:14-20; PTX 514 at 200.)

Sandoz's Response:

SEC cannot be used to determine molecular weight directly, because "[b]y itself, a size exclusion chromatography column has no ability to measure molecular weight." (Sept. Tr. 1221:9-10 (Scandella).) Instead, following the SEC run, the molecular weights of the separated material can be estimated with an online detector, such as a light scattering detector, or through the use of a calibration curve. (Sept. Tr. 1211:25-1212:17 (Scandella); DTX 3581 at 7.) Moreover, "[w]hatever number you get out of [the SEC] column is relative to how you standardize the column." (Sept. Tr. 1181:14-16; 1221:22-23 (Scandella).) Dr. Scandella made clear at trial that "[t]he SEC technique is not an absolute technique. It never gives an absolute number" for molecular weight. (Sept. Tr. 1205:20-23; 1221:19-25 (Scandella); 1762:25-1763:4 (Wall).) For copolymer-1, the molecular weights and molecular weight distributions measured by SEC vary significantly depending on the calibration standards used. (*See, e.g.*, DTX 3581 at 12; Sept. Tr. 1224:22-1227:4; 1259:13-1260:15 (Scandella).) None of the SEC literature in 1994 taught how to determine the molecular weight of a mixture as complex as copolymer-1. (*See, e.g.*, Sept. Tr. 1812:17-22; 1820:25-1821:19 (Wall).) *See* Sandoz's Responses to ¶¶ 194, 209, 451, 466, 475, 489, and 497, which are incorporated by reference.

211. SEC analysis utilizes a size exclusion (or gel filtration) column, which is a gel-filled glass or metal cylinder where the separation of molecules takes place. (Sept. Tr. (Grant) 198:4-8, 198:24-199:25; PTX 986 at 10-11.)

Sandoz's Response:

Undisputed.

212. The sample to be analyzed is introduced into the top of the column along with liquid which carries the sample down through the gel. (Sept. Tr. (Grant) 200:1-13; PTX 986 at 12-13.) The individual beads making up the separation gel have many pores of varying sizes. Size exclusion takes place because large molecules cannot get into the pores, and therefore pass through quickly, while smaller molecules can go into the pores to various extents, and therefore travel a longer path through the column and come out later than the larger molecules. (Sept. Tr. (Grant) 199:12-25, 200:14-201:7; PTX 986 at 14-15.) For this reason, molecules of different

sizes are separated from one another as they travel through the column.

Sandoz's Response:

Factors other than size can influence the retention time in the SEC column, including molecular shape and "interaction between the column matrix and the sample, for example, ion exchange interactions." (Sept. Tr. 1199:22-1200:4 (Scandella).) As Dr. Scandella explained at trial, copolymer-1 is likely have more than one shape in solution. (Sept. Tr. 1200:14-18; DTX 3581 at 6.) Teva's measurements from 1993 demonstrate that copolymer-1 has secondary structure and is not a random coil. (DTX 1113 at TEV000312034.) In particular, Teva's results show that "[r]elatively high α-helical conformation (secondary structure) of COP-l was determined by circular dichroism and confirmed by FT-IR. A non-random distribution of helicity was found …. [I]n spite of a random synthesis, COP-l is, essentially, a mixture of polypeptides having a non-random primary structure of a certain α-helix secondary structure." (DTX 1113 at TEV000312034; Sept. Tr. 1202:11-1204:4 (Scandella).) *See* Sandoz's Response to ¶ 194, which is incorporated by reference.

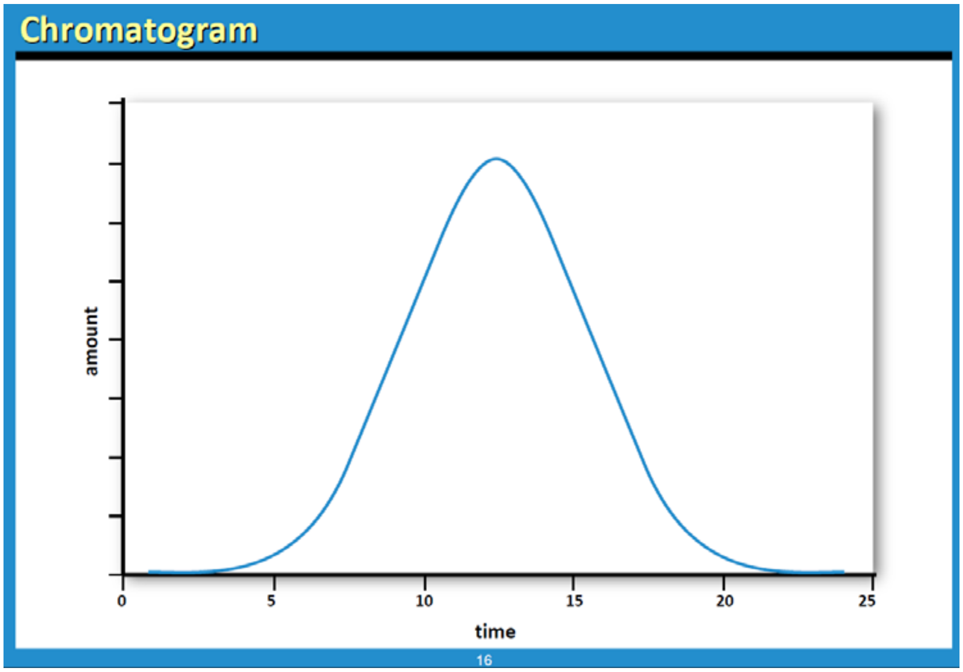
213. The bottom of the column is connected through a tube to a detector, which detects the presence and the quantity (amount) of molecules exiting the column. (Sept. Tr. (Grant) 201:8-24.)

Sandoz's Response:

Undisputed.

214. The output of the detector is a graph, called a chromatogram, which is plotted on the x-axis as time and on the y-axis as the amount of the material passing the detector at each point in time. (Sept. Tr. (Grant) 201:25-203:19; PTX 986 at 16.) Larger molecules exit the column first due to the size exclusion. (Sept. Tr. (Grant) 200:23-201:7; PTX 986 at 13.) The highest point, or peak, of the chromatogram, represents the time at which the species of molecules present in the highest abundance pass by the detector. (Sept. Tr. (Grant) 1404:23-1405:9; PTX 969 (Svec Dep.) at 9:19-23; PTX 982.)

Figure 1



(PTX 986 at 16.)

Sandoz's Response:

Factors other than size can influence the retention time in the SEC column, including molecular shape and "interaction between the column matrix and the sample, for example, ion exchange interactions." (Sept. Tr. 1199:22-1200:4 (Scandella).) *See* Sandoz's Response to ¶ 212, which is incorporated by reference.

215. In order to determine the molecular weight of the molecules exiting the column at each point (or time) along the chromatogram, it is necessary to have a calibration curve, which correlates the time at eqach point along the chromatogram's x-axis with the molecular weight of material exiting the column at that particular time. (Sept. Tr. (Grant) 203:20-204:3.)

Sandoz's Response:

Undisputed with respect to molecular weight determination using SEC with a calibration curve.

216. SEC calibration was well-understood in 1994. (Sept. Tr. (Grant) 204:4-5.) By that time, it was well-known in 1994 that to create a calibration curve, calibration standards—molecules of known molecular weights—had to be run through the column to determine the time

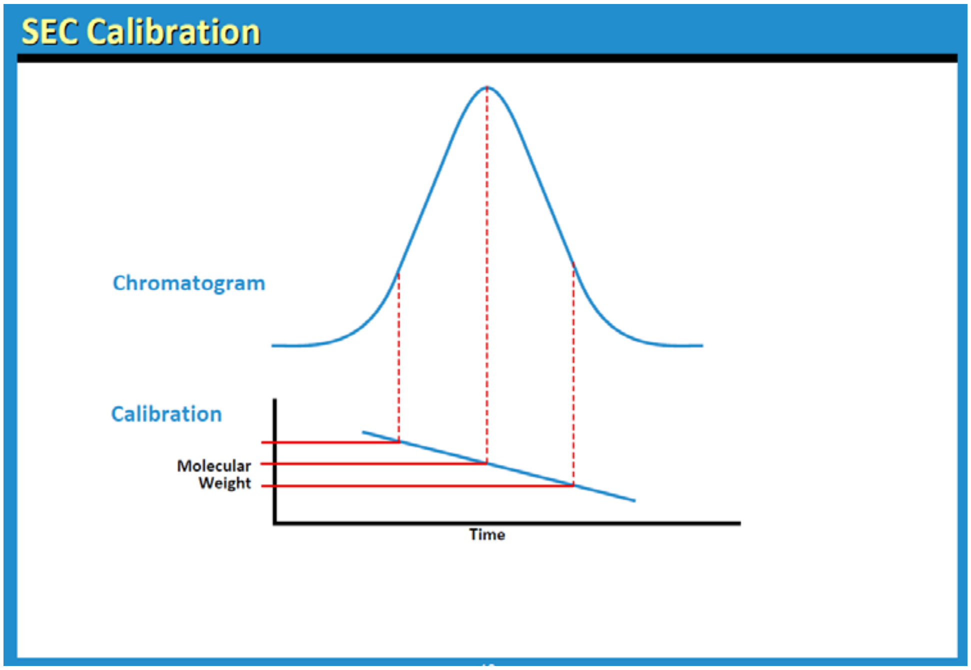
that they exited the SEC apparatus. The molecular weight of each standard, which can be determined by a number of independent (non-SEC) methods, is plotted against the time the standard comes out of the column. (Sept. Tr. (Grant) 204:6-205:10; PTX 986 at 17.)

Sandoz's Response:

For copolymer-1, the molecular weights and molecular weight distributions measured by SEC vary significantly depending on the calibration standards used. (*See, e.g.*, DTX 3581 at 12; Sept. Tr. 1224:22-1227:4; 1259:13-1260:15 (Scandella).) And the measured molecular weights of certain standards, particularly copolymer-1 self-standards, also vary significantly depending on the analytical method that is used. (*See* Sandoz's Opening FFCOL ¶¶ 123-132.) None of the SEC literature in 1994 taught how to determine the molecular weight of a mixture as complex as copolymer-1. (*See, e.g.*, Sept. Tr. 1812:17-22; 1820:25-1821:19 (Wall).) *See also* Sandoz's Responses to ¶¶ 194, 209, 451, 466, 475, 489, and 497, which are incorporated by reference.

217. To determine the molecular weight at any point (*e.g.*, the peak) on the chromatogram, one can match the time from the x-axis to the corresponding time on the calibration curve and read the molecular weight from the y-axis of the calibration curve. (Sept. Tr. (Grant) 205:11-206:2; PTX 986 at 18.)

Figure 2



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Sandoz's Response:

For copolymer-1, the molecular weights and molecular weight distributions measured by SEC vary significantly depending on the calibration standards used. (*See, e.g.*, DTX 3581 at 12; Sept. Tr. 1224:22-1227:4; 1259:13-1260:15 (Scandella).) And the measured molecular weights of copolymer-1 self-standards also vary significantly depending on the analytical method that is used. (*See* Sandoz's Opening FFCOL ¶¶ 123-132.) As a result, different calibration curves are obtained for the same self-standards, leading to different estimated molecular weights for a given copolymer-1 sample when copolymer-1 self-standards are used. (*See, e.g.*, Sandoz's Responses to ¶ 462, 466, 474 and 475; DTX 3581 at 16.)

218. It was known in 1994 that there were at least two options for calibrating an SEC column to get accurate molecular weights for a polypeptide mixture like copolymer-1: the conventional way was to use calibration standards that have the same relationship between size and shape in solution (also known as "hydrodynamic volume") and molecular weight as the sample being measured, and the other was to use a method called "universal calibration." (Sept. Tr. (Grant) 206:3-208:20, 1399:18-1400:13; PTX 969 (Svec Dep.) at 94:21-95:5; PTX 990 at 2.)

Sandoz's Response:

The term "accurately" is not defined in this paragraph nor in the cited testimony and is not part of the Court's claim construction for the "molecular weight" limitations. To the extent Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is misguided. As Sandoz's experts testified, "SEC doesn't yield absolute molecular weights. It's not an absolute measurement method. So one wouldn't assume that the value that came from a size exclusion column was an absolute value." (Sept. Tr. 1292:21-1293:1 (Scandella); 1825:1-4 (Wall).) In addition, in using SEC to obtain molecular weight data, it is not necessary for the standards to have the same hydrodynamic volume as the sample being analyzed. (Sept. Tr. 1292:13-15 (Scandella).) As Dr. Scandella testified:

> Often one doesn't know what the hydrodynamic volume of a sample is, and in the biotechnology industry size exclusion chromatography is used

> normally using protein standards, and one reports the results as relative to the protein standards, understanding that the shape of the molecule that you're studying may not be exactly the same as the protein standards.

(Sept. Tr. 1292:15-20 (Scandella).) Sandoz's experts also explained that neither the use of self-standards nor universal calibration would have enabled the claims. (Sandoz's Opening FFCOL ¶¶ 122-142.) Moreover, universal calibration was not a common and widespread technique in the field of biotechnology and pharmaceutical products in 1994 or 1995. (Sept. Tr. 1284:13-18 (Scandella).).

219. The necessity of matching the hydrodynamic characteristics of the sample and the calibration standards in conventional SEC calibration was well-known to those of skill in the art and well-described in the literature in 1994. (Sept. Tr. (Grant) 1412:6-1413:16; Sept. Tr. (Scandella) 1314:15-1316:24; PTX 961 (Kota Dep.) at 18:3-14; PTX 962 (B. Rao Dep.) at 75:6-76:10, 78:14-80:5; PTX 973 (Venkataraman Dep) at 108:20-109:23; PTX 974 (Wallingford Dep.) at 146:9-149:7; PTX 317 at MYL0000111; PTX 553 at 72.) For example, Janson 1989 states that "[t]he relationship between size and molecular weight of solutes is strongly dependent upon solute shape. . . . It is readily seen that calibration versus molecular weight is only meaningful for solutes of similar shape." (PTX 553 at 72.)

Sandoz's Response:

See Sandoz's Responses to ¶ 218 and 448, which are incorporated by reference.

220. On the other hand, if standards that match the hydrodynamic volume to molecular weight characteristics of the sample were unavailable, it was also well known that universal calibration could be used to determine an accurate molecular weight for a sample. (Sept. Tr. (Grant) 208:14-20, 1399:18-1400:13, 1401:12-18, 1413:17-23; PTX 970 (Svec Dep.) at 320:2-321:10, 326:14-327:10.)

Sandoz's Response:

See Sandoz's Responses to ¶ 218 and 448, which are incorporated by reference.

221. Universal calibration does not require the standards to have the same hydrodynamic volume to molecular weight relationship as the sample, because it uses a different physical property (intrinsic viscosity) to allow a correlation of the size of molecules exiting the column to their molecular weight. (Sept. Tr. (Grant) 208:14-20, 1400:6-15.)

Sandoz's Response:

See Sandoz's Responses to ¶ 488, which is incorporated by reference.

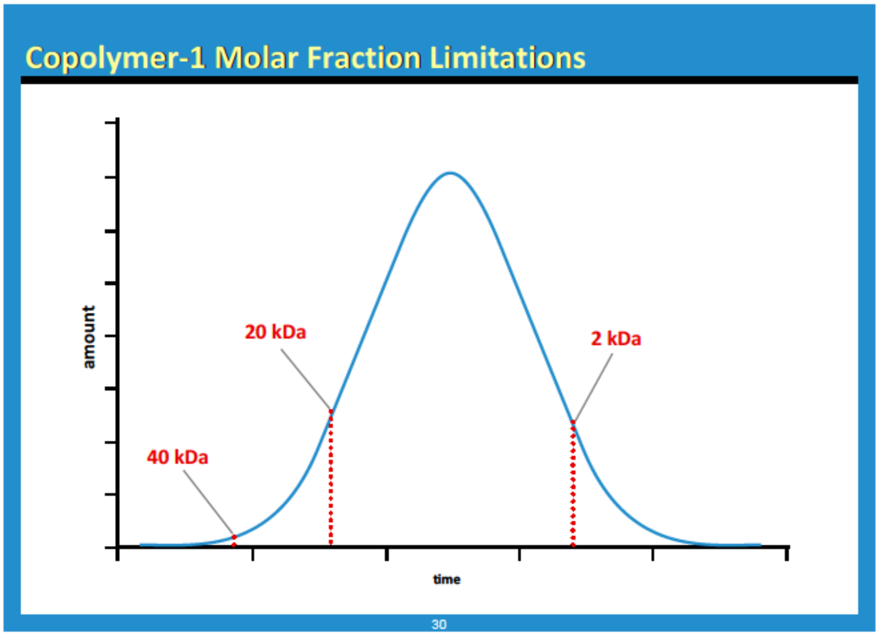
222. In addition to allowing determination of an average molecular weight, SEC allows the separation of molecules and the determination of the percentage of molecules having molecular weights falling within any given molecular weight range. (Sept. Tr. (Grant) 209:17-25, 227:8-22; PTX 986 at 33.)

Sandoz's Response:

Determination of the percentage of molecules having molecular weights falling within any given molecular weight range requires the use of SEC calibration standards, and the values will vary significantly depending on the calibration standards used. (*See, e.g.*, DTX 3581 at 12; Sept. Tr. 1224:22-1227:4; 1259:13-1260:15 (Scandella).) *See* Sandoz's Response to ¶ 210, which is incorporated by reference.

223. A chromatogram represents the amount of material that is exiting the size exclusion column at any particular time (as reflected on the x-axis). The chromatogram represents the entirety of the molecules in the sample. (Sept. Tr. (Grant) 203:14-19.) On the illustrative chromatogram shown below, the molecular weights of 40 kDa, 20 kDa, and 2kDa are depicted from left to right because large molecules come out of the size exclusion column earlier than smaller molecules. (Sept. Tr. (Grant) 227:8-22; PTX 986 at 30.)

Figure 3



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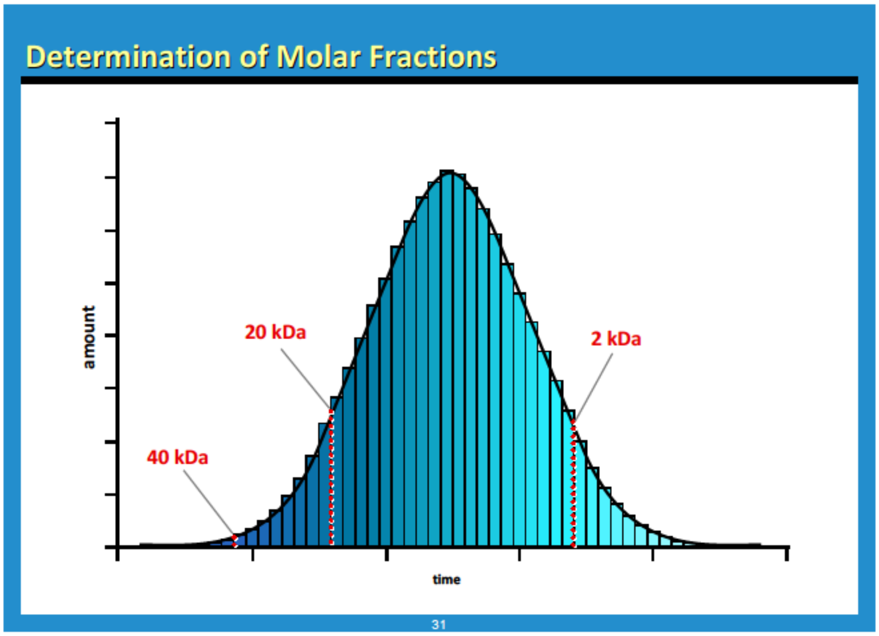
Sandoz's Response:

Factors other than size can influence the retention time in the SEC column, including molecular shape and "interaction between the column matrix and the sample, for example, ion exchange interactions." (Sept. Tr. 1199:22-1200:4 (Scandella).). *See* Sandoz's Response to ¶ 212, which is incorporated by reference. Moreover, the 2, 20, and 40 kDa depicted in the figure are average molecular weights of the material in that section of the chromatogram, because even the smallest sample of copolymer-1 that can be analyzed contains billions of molecules with different individual molecular weights. (Sept. Tr. 1193:24-1194:11; 1225:18-1226:1 (Scandella).) There is no analytical methodology, today or in 1994, capable of isolating and measuring a single molecule of copolymer-1. (Sept. Tr. 1225:13-17 (Scandella).) And these values are relative to and dependent on the calibration standards that are used. (Sept. Tr. 1213:17-24; 1221:19-25 (Scandella); 1762:25-1763:4; 1765:19-20; 1806:1-4 (Wall); 289:12-16 (Grant); DTX 4016 at 95:4-24 (Gad); DTX 3581 at 8.) *See* Sandoz's Responses to ¶¶ 447, 448, 458, 485, and 513, which are incorporated by reference.

224. In order to calculate the percentage of species having a molecular weight within a certain range, the chromatogram is divided into slices, which can be represented by small rectangles, as shown in the figure below. A molecular weight is assigned to each slice through the use of a calibration curve. The number of moles of the material, which represents the number of molecules, in each slice can be calculated by dividing the amount of the material in the slice by the molecular weight that has been assigned to that slice. (Sept. Tr. (Grant) 228:11-229:11, 230:8-12; PTX 986 at 31.)

Figure 4



Sandoz's Response:

Each slice represents an average molecular weight with an unknown number of copolymer-1 molecules of varying molecular weights and sequence. (Sept. Tr. 297:17-24 (Grant).) *See also* Sandoz's Response to ¶ 223, which is incorporated by reference.

225. The number of moles (*i.e.*, the number of molecules) of all of the molecules falling within a molecular weight range, *e.g.*, between 2 kDa and 20 kDa, can be added together and divided by the total number of moles of all of the molecules present in the sample, as represented by the entire chromatogram. Multiplying this fraction by 100 gives the percentage (on a "molar fraction" basis) of molecules within the molecular weight range. Similarly, the molar percentage of molecules having molecular weights of above 40 kDa can be calculated by dividing the number of moles of material having molecular weight of above 40 kDa by the total number of moles of the materials represented by the entire chromatogram. (Sept. Tr. (Grant) 229:12-230:7; PTX 986 at 32.)

Sandoz's Response:

See Sandoz's Responses to ¶¶ 223-224, which are incorporated by reference.

226. When using this method, it is not necessary to know how many different molecular weights are in each slice. It is acceptable to assign a single molecular weight to each slice. (Sept. Tr. (Grant) 298:11-299:3, 329:6-330:7; PTX 986 at 31.)

Sandoz's Response:

See Sandoz's Responses to ¶¶ 223-224, which are incorporated by reference.

V. LEVEL OF ORDINARY SKILL IN THE ART

227. Dr. Grant has defined a person of ordinary skill in the art as having an "advanced degree or equivalent in a chemical or biological discipline and significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides." The person of ordinary skill in the art also "has access to and the ability to consult with other scientists having related and/or complementary knowledge and experience in the areas of polymer chemistry, biochemistry, analytical chemistry, separation technology, medicine, and toxicology." (Sept. Tr. (Grant) 189:19-190:6, 1398:11-17; PTX 986 at 3.)

Sandoz's Response:

Sandoz does not dispute that this was Dr. Grant's testimony at trial.

228. Defendants' expert witnesses have similarly defined the level of skill in the art as being high. (Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9; Sept. Tr. (Wall) 1756:2-12; Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4.)

Sandoz's Response:

Sandoz's experts define a person of ordinary skill as someone containing training and a certain amount of experience. Sandoz disagrees with the characterization of the level of ordinary skill as "high" as opposed to "low" or any other relative description.

229. For example, Sandoz's expert Dr. Scandella defined a person of ordinary skill in the art as having a Ph.D. in chemistry, biochemistry or related field with a minimum of three years of experience in chromatography, and specifically in size exclusion chromatography of macromolecules. (Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9.)

Sandoz's Response:

Undisputed.

230. Sandoz's expert Dr. Wall defined a person of ordinary skill in the art as having a Ph.D. in chemistry or biochemistry or related field with three years of experience in chromatography or a person who has supervised or directed a research lab that conducts chromatography. (Sept. Tr. (Wall) 1756:2-12.)

Sandoz's Response:

Undisputed.

231. Mylan's expert Dr. Zeiger testified that he has "no problem" with Dr. Grant's definition of a person of ordinary skill in the art. (Sept. Tr. (Zeiger) 811:15.) Dr. Zeiger himself defined a person of ordinary skill as: "A person of ordinary skill in fields of biochemistry and immunology in 1994 would have had an advanced degree in a chemical or biological discipline, and extensive experience in the synthesis, fractionation, and characterization of polymers, such as their hydrodynamic and structural properties, as applied to proteins, synthetic peptides and/or polydisperse peptide mixtures, as well as experience in the determination of the molecular weight distribution and average molecular weights of such polymers by methods such as size exclusion chromatography (SEC), and an understanding of how the standards and conditions used in the molecular weight determination affect the results obtained." (Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4.)

Sandoz's Response:

Undisputed.

232. The Court credits Dr. Grant's testimony and adopts his proposed definition of the level of ordinary skill in the art. Nonetheless, in light of the nearly identical view of the level of ordinary skill in the art put forward by the parties' experts, the Court's analysis of the legal and factual issues, as set forth below, is the same regardless of which definition is used.

Sandoz's Response:

Sandoz agrees that the Court's analysis of the legal and factual issues, as set forth below, is the same regardless of which definition is used.

VI. FINDINGS OF FACT AND CONCLUSIONS OF LAW RELATING TO INFRINGEMENT

Sandoz's Responses to Teva's Proposed Findings of Fact on Infringement

233. Plaintiffs presented evidence at trial that Defendants' proposed products meets each and every limitation of the asserted claims. Mylan largely does not contest infringement, with the exception of its assertion that its product is not "copolymer-1." Sandoz similarly does not contest that its proposed product meets almost every limitation of the asserted claims. Sandoz asserts only that its product is not "copolymer-1" and that the process [redacted] does not include in Step 2 a time "predetermined by a test reaction."[e] Sandoz's claim that its product is not copolymer-1 was made for the first time on the eve of trial, and Sandoz proffered no evidence to support it. Sandoz does not dispute that its current ANDA process, and the process in the Briefing Book, should that be proposed and accepted by the FDA, includes a time "predetermined by test reaction." For the reasons set forth below, Mylan's and Sandoz's proposed products infringe each of the asserted claims.

Sandoz's Response:

For the reasons set forth below and in Sandoz's Proposed Findings of Fact and Conclusions of Law Nos. 1-39, after comparing the construed claims to Sandoz's proposed product, Teva has failed to prove that Sandoz's proposed product and process meet each limitation of the asserted claims of the patents-in-suit.

A. Teva's Asserted Legal Principles

234. A finding of patent infringement is a two-step process. First, the claims must be construed by the court as a matter of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). The inquiry is an objective one. A court must determine "what one of ordinary skill in the art at the time of the invention would have understood the term to mean." *Id.* at 986. On August 29, 2011, the Court issued its claim construction decision, construing the disputed claim terms. (D.I. 275.) The Court will apply its prior construction of each claim term to determine infringement, as set forth below.

Sandoz's Response:

Sandoz does not dispute the content of Teva Finding of Fact No. 234, but draws the Court's attention to its proposed findings of fact and post-trial memorandum on claim construction. (Sandoz's Opening FFCOL ¶¶ 24-32; Sandoz's Post-Trial Claim Construction Memorandum.)

235. Second, the construed claims must be compared to the accused product or process to determine whether all of the limitations of at least one claim are present, either literally or by an equivalent. *Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 804 (Fed. Cir. 2007) (citing *Markman*, 52 F.3d at 976); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1323 (Fed. Cir. 2002).

Sandoz's Response:

Undisputed.

236. The doctrine of equivalents prevents an accused infringer from avoiding claim limitations by making minor or insubstantial changes to the accused product to avoid infringement while retaining the identity of the invention. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 564 (Fed. Cir. 2000), *vacated on other grounds by* 535 U.S. 722 (2002). This Court has noted that the doctrine of equivalents is used to "temper unsparing logic and prevent an infringer from stealing the benefit of the invention." *Astra Aktiebolag v. Andrx Pharms., Inc.*, 222 F. Supp. 2d 423, 504 (S.D.N.Y. 2002) (quoting *Festo*, 234 F.3d at 564

(Fed. Cir. 2000)). An accused product infringes under the doctrine of equivalents if the limitations of the claim are insubstantially different from the accused product. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1351 (Fed. Cir. 2003); *Eagle Comtronics v. Arrow Commc'n Labs.*, 305 F.3d 1303, 1315 (Fed. Cir. 2002).

Sandoz's Response:

Teva accuses Sandoz of raising defenses on the eve of trial, but Teva has now presented a new theory for the first time in its post-trial briefing.[1] As Sandoz pointed out in its Summary of Defenses submitted with the Joint Pretrial Order, at that time Teva had not identified any specific claim limitations on which it intended to argue infringement under the doctrine of equivalents. (Jt. Pretrial Order, Dkt. 271, at 11.) Then, just before trial, Teva designated an expert to testify on the doctrine of equivalents with respect to the "copolymer-1" limitation, but not equivalence of Sandoz's process to the "predetermined by test reaction" limitation. (*See* Teva's Opening FFCOL ¶ 86.) Further, Teva did not ask Dr. Gokel, its expert on literal infringement of the "predetermined by test reaction" limitation, any questions about the doctrine of equivalents.

It would be highly prejudicial to Sandoz to allow Teva to present a wholly new doctrine of equivalents argument after trial has concluded, as Sandoz would be denied the opportunity to cross-examine Teva's experts on this theory. The Court should not consider Teva's untimely argument that Sandoz's proposed glatiramer acetate infringes under the doctrine of equivalents.

Even if the Court does consider Teva's doctrine of equivalents argument, Sandoz's proposed glatiramer acetate product does not infringe. *See* Sandoz's Opp. Nos. 419-421, *infra.*

237. Pursuant to 35 U.S.C. § 271(b), "[w]hoever actively induces infringement of a patent shall be liable as an infringer." To establish a claim of induced infringement, a patentee must show by the preponderance of the evidence that the accused infringer knowingly induced infringement and had a specific intent to encourage another's infringement. *E.g., AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010).

[1] Dr. Gokel included a single conclusory paragraph on the doctrine of equivalents as it relates to the "predetermined by test reaction" limitation in his supplemental expert report, served August 29, 2011, but Teva did not include this argument in its statement of claims and defenses.

Sandoz's Response:

Undisputed.

238. Infringement must be shown by a preponderance of the evidence, which requires showing that it is more likely than not that infringement has occurred. *See Enercon GmbH v. ITC*, 151 F.3d 1376, 1384 (Fed. Cir. 1998); *In re Omeprazole Patent Litig.*, 490 F. Supp. 2d 381, 414 (S.D.N.Y. 2007).

Sandoz's Response:

Undisputed.

B. Teva's Proposed Findings of Fact

(i) Mylan's ANDA Product (omitted from Sandoz's opposition)

(ii) Sandoz's ANDA Product

(1) Active Ingredient

278. The active ingredient in Sandoz's proposed product is described as glatiramer acetate. (Sept. Tr. (Gokel) 360:16-18.) As Sandoz and Momenta have acknowledged, glatiramer acetate is also known as copolymer-1. For example, Sandoz's labeling for its proposed product describes its active ingredient as "glatiramer acetate (formerly known as copolymer-1)." (Sept. Tr. (Lisak) 141:13-143:19; PTX 206 at SDZ00000031.) Sandoz internal documents likewise make clear that one of the names for its active ingredient is "copolymer-1." (Sept. Tr. (Grant) 220:13-221:7; PTX 141 at MMT00391607.) In addition, Momenta scientist Mani Iyer, who was in charge of manufacturing and developing Sandoz's glatiramer acetate, specifically testified that Sandoz's product is a "copolymer-1 composition." (PTX 960 (Iyer Dep.) at 25:8-10.)

Sandoz's Response:

Sandoz disputes that its proposed product is "copolymer-1" as construed by the Court. Sandoz's product does not meet the 6:2:5:1 molar ratio requirement. *See* Sandoz Response ¶¶ 279-281, and Sandoz's Opening FFCOL ¶¶ 14-18, 33-36 and 39.

Teva is exaggerating the role Dr. Iyer played in the development of Sandoz's proposed product in an effort to ascribe additional meaning to his statements. Dr. Iyer, far from being "in charge" of manufacturing and developing Sandoz's proposed product, reported to both Dr. Bishop and Dr. Pat Oliver. Tellingly, Dr. Iyer never had any communications with any of the

Sandoz personnel assigned to the glatiramer acetate product. (PTX 960 (Iyer Dep.) 111:4-20.) He was involved in the manufacture, but not the strategy for design or development, of Sandoz's proposed glatiramer acetate product.

Dr. Iyer's deposition was taken almost two years before this Court issued its claim construction order, and he could not have based any of his testimony on the constructions articulated by the Court. *See Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1270 (Fed. Cir. 1986), *cert. denied*, 479 U.S. 1030 (1987) (opinion on ultimate issue of infringement must be based on claim construction order). The term "copolymer-1" has been used in many different ways over the decades, but it has a special meaning in the patents asserted this case—a meaning that Dr. Iyer could not have been referring to in his deposition. The testimony of a single Momenta fact witness, one of several members of a team that worked on the glatiramer acetate project (*See* Sandoz's Response to ¶ 293), is insufficient to prove that Sandoz's proposed product meets the "copolymer-1" claim limitation by a preponderance of the evidence.

(a) Amino Acid Composition

279. The glatiramer acetate active ingredient in Sandoz's proposed product is composed of the four amino acids glutamic acid, alanine, lysine and tyrosine. (Sept. Tr. (Gokel) 414:23-415:9; PTX 219 at SDZ00002024-25; PTX 351 at SDZ00018614.)

Sandoz's Response:

Undisputed for purposes of this section. Sandoz's product also includes, among other things, a certain amount of bromotyrosine.

280. Sandoz's ANDA provides data on the relative proportions of glutamic acid, *alanine*, lysine and tyrosine in its proposed product, expressed as molar fractions. (Sept. Tr. (Gokel) 417:19-22, 420:12-17; PTX 219 at SDZ00002025; PTX 913 at 28.) According to Sandoz's ANDA, the lots it produced have the following molar fractions of glutamic acid, alanine, tyrosine and lysine, respectively: drug substance lots 077K7277, 0.147: 0.436: 0.083: 0.334; drug substance lot 087K7253, 0.142: 0.419: 0.083: 0.356; drug product lot CT0743, 0.134: 0.444: 0.083: 0.340; and drug product lot CT0750, 0.126: 0.421: 0.083: 0.370. (Sept. Tr. (Gokel) 416:14-419:6; PTX 219 at SDZ00002025; PTX 987 at 89.)

<u>*Sandoz's Response:*</u>

Teva states that Sandoz's ANDA provides information on the relative proportions of the amino acids in its proposed product, but this is misleading; Sandoz has recently provided updated information to the FDA showing altered proportions. (Sept. Tr. 1093:17 – 1094:3 (Bishop); PTX 913.) The molar ratio described above is no longer accurate, and the post-approval product to be marketed by Sandoz will contain a different molar ratio as described in Sandoz's Findings of Fact and Conclusions of Law ¶¶ 14-18, 33-36 and 39. (Sept. Tr. 1093:17 – 1094:3 (Bishop).); PTX 913-R, at 28, Table 6.)

281. [redacted] (Sept. Tr. (Gokel) 420:3-17.) The molar fractions of glutamic acid, alanine, tyrosine, and lysine for this lot are [redacted] (Sept. Tr. (Gokel) 420:3-17; Sept. Tr. (Sampson) 546:22-547:15; PTX 913 at 28; PTX 987 at 93-95; PTX 988 at 3.) Sandoz has not formally amended its ANDA or manufacturing process to reflect this molar fraction.

<u>*Sandoz's Response:*</u>

The FDA did not approve Sandoz's ANDA with the molar fraction ranges listed in Sandoz's 2007 ANDA [redacted]. Dr. Bishop testified that future lots of Sandoz's proposed product will be made according to Sandoz's current 1.1.0 specifications, [redacted] (Sept. Tr. 1094:20 – 1095:9, 1095:24-1096:1 (Bishop); PTX-913, at 28, Table 6.) Dr. Bishop also confirmed that Sandoz's plan to abandon its former method, which results in batches with molar ratios as listed in its original ANDA, has been communicated to the FDA. (Sept. Tr. 1105:1-5.) Teva presented no evidence that the FDA has objected to or rejected Sandoz's new ranges for its proposed product. *See* Sandoz's Response to ¶ 23.

(b) Molecular Weight

282. Sandoz's proposed product has a specification for peak average molecular weight between 5,000 and 9,000 daltons. (Sept. Tr. (Grant) 222:6-17.)

Sandoz's Response:

The patents-in-suit require both a peak molecular weight within a claimed range and a weight average molecular weight less than 10 kDa. (*See* Sandoz's Post-trial Claim Construction Memorandum; Sandoz's Opening FFCOL ¶¶ 24-32.) The weight average molecular weight for the most recent lot of glatiramer acetate manufactured according to Process 1.1.0 and reported to the FDA is [redacted] daltons. (PTX 913-R at 53.)

283. As set forth in Figure 8 below, the data in Sandoz's ANDA demonstrates that each *of* its lots falls within the specified 5,000-9,000 daltons range. (Sept. Tr. (Grant) 222:6-17; PTX 349 at SDZ00017949; PTX 351 at SDZ00018608-611; PTX 986 at 26.)

Figure 8

Lot	Peak Average Molecular Weight (Da)
077K7277	8407
087K7253	7275
058K7278	7216
078K7276	7104
128K7276	5932
029K7279	7641
049K7275	6977
049K7276	7366
059K7275	7199
CT0743	8274
CT0750	7417

Source: PTX 351 at SDZ00018608-11;
PTX 349 at SDZ00017949

Sandoz's Response:

The patents-in-suit require both a peak molecular weight within a claimed range and a weight average molecular weight less than 10 kDa. In its earlier submissions to the FDA, Sandoz identified six specific lots of proposed glatiramer acetate. (PTX 349-R at SDZ00017953.) The Mw of those six lots were 11,921; 10,993; 11,516; 10,455; 10,469; and 10,517 daltons. *Id.*

284. Sandoz determined these peak molecular weight values using SEC with TSK gel G 3,000 and G 2,000 columns. (Sept. Tr. (Grant) 214:19-215:5.) Sandoz calibrated the SEC columns using nine peptide standards that (i) had amino acid compositions consistent with the composition of copolymer-1 and (ii) had the same size-to-molecular weight relationship as copolymer-1. (Sept. Tr. (Grant) 215:6-13.)

Sandoz's Response:

Dr. Grant, reading from a Sandoz document, actually said that "[n]ine peptide reference standards with amino acid compositions consistent with glatiramer acetate covering the molecular weight range from 1,500 daltons to 12,000 daltons are used to calibrate the retention time axis in order to determine an accurate measurement of Mp." (Sept. Tr. 215:9-13.) The asserted patents include claims directed to copolymer-1 wherein a percentage of the copolymers in the mixture have molecular weights up to 40 kDa and above. Sandoz's peptide standards at best only covered copolymers up to 12 kDa. Moreover, Sandoz no longer uses the method described in No. 284.[2]

285. In addition to having a specified peak molecular weight, Sandoz's product also has particular molecular weight distribution characteristics. (Sept. Tr. (Grant) 230:13-233:14; PTX 986 at 33.)

Sandoz's Response:

Undisputed.

286. Dr. Grant used electronic molecular weight data generated by Sandoz during its SEC measurements of five Sandoz drug substance lots to calculate the percentage (on a molar fraction basis) of the copolymer-1 molecules in each lot that have a molecular weight between 2 and 20 kilodaltons and the percentage having molecular weights above 40 kilodaltons. (Sept. Tr. (Grant) 230:13-233:14.) These percentages are listed in Figure 9 below.

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[2] At trial, Sandoz, through Dr. Bishop, attempted to explain its decision to discontinue use of the Gad standards, but Teva objected, and the Court sustained the objection. (Sept. Tr. 1522:15-21.) As Teva is fully aware, however, Sandoz no longer uses these standards to measure the molecular weight of its proposed glatiramer acetate product.

Figure 9

	% molar fraction between 2 and 20 kilodaltons (%)	% molar fraction above 40 kilodaltons (%)
077K7277	≥ 91.99	≤ 0.36
087K7253	≥ 85.00	≤ 0.28
049K7275	≥ 90.82	≤ 0.23
049K7276	≥ 87.36	≤ 0.24
059K7275	≥ 88.83	≤ 0.25

Source: PTX 377

Sandoz's Response:

Teva asserts that Dr. Grant "calculated" the percentage of copolymer-1 molecules in each lot that have a molecular weight between 2 and 20 kDa and the percentage having molecular weights above 40 kDa. At best, Dr. Grant *estimated* this percentage, as he himself admitted that his method only results in a percentage that is "representative." (Sept Tr. 299:4-20.) Dr. Scandella repeatedly emphasized that the percent of species above or below a certain molecular weight, when determined by SEC, can only be estimated, and confirmed that this was "well known in the field." (Sept. Tr. at 1205:20-1206:14, 1226:2-8.)

Sandoz does not dispute that Dr. Grant has estimated that its proposed glatiramer acetate product has over 75% of its molar fraction within an average molecular weight range of 2 to 20 kDa, and less than 5% above 40 kDa. However, Sandoz does not agree with Dr. Grant's characterization that the claims describe a percentage of *individual molecules* having molecular weights between 2 and 20 kDa or above 40 kDa. The range between 2 and 20 kDa and above 40 kDa represents a range of average molecular weights. (Sept Tr. 1193:24-1194:11, 1224:22-1225:23 (Scandella); 297:4-299:16 (Grant).)

287. Using the electronic molecular weight data for the same five Sandoz drug

substance lots, Dr. Grant also calculated the molar fraction percentages of molecules having molecular weights between 2 and 20 kilodaltons in the TFA copolymer-1 intermediate that corresponded to each lot. (Sept. Tr. (Grant) 236:22-239:4; PTX 986 at 40.) These percentages are listed in Figure 10 below.

Figure 10

Trifluoroacetyl copolymer-1 corresponding to sample	% TFA molar fraction between 2 and 20 kilodaltons (%)
077K7277	≥ 91.45
087K7253	≥ 89.69
049K7275	≥ 92.82
049K7276	≥ 91.34
059K7275	≥ 92.07

Source: PTX 377

<u>*Sandoz's Response:*</u>

Teva asserts that Dr. Grant "calculated" the percentage of TFA copolymer-1 molecules in each lot that have a molecular weight between 2 and 20 kDa. At best, Dr. Grant *estimated* this percentage, as he himself admitted that his method only results in a percentage that is "representative." (Sept Tr. 299:4-20.) Dr. Scandella repeatedly emphasized that the percent of species above or below a certain molecular weight molecular weight values determined by SEC can only be estimated and that this was "well known in the field." (Sept. Tr. 1205:20-1206:14, 1226:2-8.)

Sandoz does not dispute that Dr. Grant has estimated that its proposed TFA copolymer-1 intermediate product has over 75% of its molar fraction within an average molecular weight range of 2 to 20 kDa. However, Sandoz does not agree with Dr. Grant's characterization that the claims describe a percentage of *individual molecules* having molecular weights between 2 and 20 kDa. The range between 2 and 20 kDa represents a range of average molecular weights. (Sept Tr. 1193:24-1194:11, 1224:22-1225:23 (Scandella); 297:4-299:16 (Grant).)

(2) Sandoz's Manufacturing Process

(a) Development of Process

Sandoz's Response:

Sandoz generally disputes Teva's focus on development activities performed by Sandoz and Momenta that cannot be found infringing as a matter of law. The Hatch-Waxman safe harbor, codified at 35 U.S.C. § 271(e)(1), exempts a party from liability for otherwise infringing acts where they involve a patented invention that is reasonably related to securing federal regulatory approval. Specifically, the statute states in relevant part:

It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

35 U.S.C. § 271(e)(1).

The Federal Circuit has adopted an especially broad view of the 271(e)(1) safe harbor in the context of ANDA litigation, repeatedly noting that the safe harbor protects a generic drug manufacturer using a patented product or process to prepare an ANDA for FDA approval and market entry. *See, e.g., Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1351 (Fed. Cir. 2004) (noting that 271(e)(1) "exempt[s] generic manufacturers from an infringement action when their use is for the purposes of developing and researching generic alternatives to obtain premarket approval by the FDA"); *Allergan, Inc. v. Alcon Labs.*, 324 F.3d 1322, 1326 (Fed. Cir. 2003) ("The exemption to infringement under section 271(e)(1) allows a generic drug manufacturer to take the steps needed to bring a generic drug to market without waiting until the patent expires"); *Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002) ("Under 35 U.S.C. section 271(e)(1), it is not patent infringement to conduct otherwise infringing acts necessary to

prepare an ANDA"); *Mylan Pharms., Inc. v. Thompson*, 268 F.3d 1323, 1326 (Fed. Cir. 2001) (same); *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1249 (Fed. Cir. 2000) (noting that 271(e)(1) "specifically provides an ANDA applicant [with] immunity from allegations of infringement for acts that are necessary in preparing an ANDA") (emphases added). The Federal Circuit recently affirmed the continuing vitality of 271(e)(1) protection for activities performed "in order to expedite development of information for regulatory approval of generic counterparts of patented products." *Classen Immunotherapies, Inc. v. Biogen IDEC*, Nos. 2006-1634, 2006-1649, 2011 U.S. App. LEXIS, at *36 (Fed. Cir. Aug. 31, 2011).

Section 271(e)(1) immunizes "all uses of patented inventions that are reasonably related" to federal regulatory submissions. *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202 (2005). There is no dispute that Sandoz's allegedly infringing activities are solely for purposes "reasonably related" to securing FDA approval to market generic Copaxone, as that is precisely what Teva has alleged throughout trial. *See, e.g.,* Teva Proposed Findings of Fact Nos. 288-300. And, following the Federal Circuit's precedent, this Court has expressly held that "acts in furtherance of filing a future ANDA" are protected by the 271(e)(1) safe harbor. *Astrazeneca AB v. Mylan Labs., Inc.*, 265 F. Supp. 2d 213, 218 (S.D.N.Y. 2003) (Jones, B.) ("[A]ny other interpretation of the statute [271(e)(1)] would be inconsistent not only with the clear language of the statutory exemption from liability, but also the policies underlying the Hatch-Waxman Act").

Indeed, Teva understands all too well that the safe harbor applies here, having relied on the Court's ruling in *Astrazeneca* to argue in another case that "no liability can be imposed for acts in furtherance of filing the ANDA." Teva's Memorandum of Points and Authorities, at 3, *Aventis Pharma S.A. v. Amphastar Pharms., Inc.*, No. EDCV-03-887 (C.D. Cal filed Apr. 26,

2004). Thus, activities performed in furtherance of Sandoz's ANDA cannot be infringing as a matter of law.

288. Before it entered into the agreement with Momenta, Sandoz had worked on developing its own process for making generic Copaxone®. Dr. Anup Ray, a principal scientist at Sandoz and its 30(b)(6) designee on Sandoz's processes for manufacturing copolymer-1, was tasked with this project. (PTX 364 (Topic 18); PTX 966 (Ray Dep.) at 18:13-15, 23:2-24:10, 30:13-16.)

Sandoz's Response:

Sandoz does not dispute Sandoz's separate development steps that are not relevant to infringement, as Sandoz's and Dr. Ray's efforts are protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra*.

289. The first thing Dr. Ray did after being given his assignment was to perform a literature search. (PTX 966 (Ray Dep.) at 32:13-15.) Following the literature search, Dr. Ray's initial strategy was to make generic Copaxone® using the method described in Teva's patent. (PTX 966 (Ray Dep.) at 42:6-15.)

Sandoz's Response:

The steps Dr. Ray took in 2005 are not relevant to infringement, as the focus must be on the process used to manufacture the product that will be marketed upon approval. Further, there is no evidence that any of Dr. Ray's work was incorporated into Sandoz's ANDA, which stemmed from work performed by Momenta, and not Sandoz. (*See* PTX 966 (Ray Dep.) at 93:16-94:3.) And, to the extent Dr. Ray did rely on the patent in forming his original strategy for manufacturing Sandoz's proposed glatiramer acetate product, those efforts would be protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

Teva also misstates Dr. Ray's testimony. When asked what his initial strategy was, Dr. Ray replied "[m]y strategy was to make that polymer and how the literature or patent is describing to make that." (PTX 966 (Ray Dep.) at 42:6-15.) When asked whether he used "literature" interchangeably with the patent, Dr. Ray defined "literature" as the "patent or any –

any literature," and specifically identified at least one article from the 1970s that he referred to in designing his process. (*See, e.g.*, *id.* at 33:2-7.) Teva's characterization of Dr. Ray's strategy as tied only to Teva's patents is misleading.

290. Dr. Ray subsequently began work on developing alternative processes for making generic Copaxone®. (PTX 889; PTX 966 (Ray Dep.) at 81:11-83:20, 108:5-19.) Sandoz's strategy was to develop a route that "circumvented" Teva's patented method. (PTX 123 at SDZ00014130.) As Dr. Ray testified, he was receiving instructions from a Sandoz lawyer on these alternative processes. (PTX 966 (Ray Dep.) at 127:8-11.)

Sandoz's Response:

The steps Dr. Ray took in 2005 are not relevant to infringement, as the focus must be on the process used to manufacture the product that will be marketed upon approval. Further, there is no evidence that any of Dr. Ray's work was incorporated into Sandoz's ANDA, which stemmed from work performed by Momenta, and not Sandoz. (*See* PTX 966 (Ray Dep.) at 93:16-94:3.) Sandoz does not dispute Dr. Ray's development process, but it is irrelevant, as Dr. Ray's efforts are protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra*. Finally, it is unremarkable that, like any pharmaceutical company attempting to manufacture a generic drug, Sandoz would try to produce an equivalent glatiramer acetate product without infringing the Orange Book patents.

291. Dr. Ray eventually devised an alternative process for making copolymer-1 that he concluded was "very different from known Teva patented process." (PTX 115; *see also* PTX 117 at SDZ00011436; PTX 966 (Ray Dep.) at 92:6-11.) Sandoz filed a patent application on this process, and Dr. Ray was a named inventor. (PTX 155.)

Sandoz's Response:

Dr. Ray's development of an alternative process for making copolymer-1 is not relevant to infringement, as the focus must be on the process used to manufacture the product that will be marketed upon approval. Further, there is no evidence that any of Dr. Ray's work was incorporated into Sandoz's ANDA, which stemmed from work performed by Momenta, and not

Sandoz. (*See* PTX 966 (Ray Dep.) at 93:16-94:3.) Dr. Ray's efforts are also protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra*.

292. Sandoz ultimately abandoned its attempts to circumvent Teva's patents and develop its own generic Copaxone® product and decided instead to collaborate with Momenta.

Sandoz's Response:

Sandoz disputes the characterization that it "attempt[ed] to circumvent Teva's patents." It is unremarkable that, like any pharmaceutical company attempting to manufacture a generic drug, Sandoz would try to produce an equivalent glatiramer acetate product without infringing the Orange Book patents. Moreover, Dr. Ray's early experiments are irrelevant, as the Court's focus must be on the product that will eventually marketed by Sandoz, and the process used to manufacture that product—not on Sandoz's efforts in 2005. Furthermore, Dr. Ray's efforts are protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra*.

293. Momenta's efforts to design a process for making generic Copaxone® were led by Dr. Mani Iyer, who was then a Principal Scientist. (PTX 960 (Iyer Dep.) at 5:20-6:9, 16:20-21, 18:3-19:10, 19:20-20:2.)

Sandoz's Response:

Dr. Iyer did not lead Momenta's efforts to design a process for making generic Copaxone. He reported to Dr. John Bishop, and was a member of a team that included Claire Coleman, Harper Kominski, Sal Marchese, Alicia Thompson and Kelly Hanson. (PTX 960 (Iyer Dep.) at 26:14-16.) In the latter part of 2006, Dr. Iyer began to report to Pat Oliver. (*Id.* at 29:17-25, 30:12-15.) At no point was he the leader of the team at Momenta tasked with developing a generic glatiramer acetate product.

294. Like Dr. Ray, the first thing Dr. Iyer did when given his assignment was to review the literature on copolymer-1, including the '808 patent. (Sept. Tr. (Bishop) 1075:19-1076:12; PTX 960 (Iyer Dep.) at 19:23-20:2, 147:9-16.) Dr. Iyer understood that Teva's method for making copoymer-1 was a "Patented Process." (PTX 135; PTX 777; PTX 960 (Iyer Dep.) at

452:12-46:19.)

Sandoz's Response:

Teva misstates Dr. Iyer's testimony as to whether he understood Teva's process to be a "patented process." Dr. Iyer actually testified that the document he created entitled "patent procedure" was based on "a compilement of a lot of literature[,]" and not just on the '808 patent, as Teva urges. (PTX 960 (Iyer Dep.) at 46:20-47:9.) Moreover, as discussed *supra* in Sandoz's Response to ¶ 278, Dr. Iyer's testimony on the ultimate issue of whether Teva's method was a "patented process" is insufficient to satisfy Teva's burden on infringement. Finally, Dr. Iyer's initial studies on how to manufacture copolymer-1 are protected under the safe harbor provision of 271(e), and are therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

295. Momenta's process development strategy is set forth in a December 2005 presentation by Dr. Iyer. (PTX 141.) Phase I of the project was to replicate the "literature process." (PTX 141 at MMT00391608, 610-614.) The "literature process" was Momenta's internal designation for Teva's patented process. (PTX 960 (Iyer Dep.) at 130:7-9, 130:11-14, 130:17.) Phase II was to modify the process to "stay outside the process claims." (PTX 141 at MMT00391608, 647-51.) Phase III was to make further modifications to "add[] additional distance from a IP standpoint." (PTX 141 at MMT00391608, 652-56.)

Sandoz's Response:

Teva is attempting to equate the "literature process" described by Dr. Iyer with the "patented process." But the record clearly shows that the "literature" relied upon by Momenta includes far more than just Teva's patents. The "literature" Dr. Bishop testifies was reviewed by his team, including Dr. Iyer, includes the package insert for Copaxone, the label for Copaxone, several publications and articles, and multiple patents and patent applications. (Sept. Tr. 1069:24-1070:2; 1070:15-20; 1071:1-15; 1072:14-24.) Specifically, Dr. Bishop testified that the "literature" uncovered by his team's initial search included the '550 patent, the 1971 Teitlebaum article, and the Gad patents, among others.

Teva asserts, based on Dr. Iyer's testimony, that "[t]he 'literature process' was Momenta's internal designation for Teva's patented process[,]" but this is a clear misstatement of his testimony. In fact, all that Dr. Iyer testified to was that the Teva patents were included in the large body of literature used by Momenta in developing its process. (PTX0960 (Iyer Dep.) at 130:7-9, 11 ("Q: The literature that you were following included the Teva patents on making low molecular weight Copolymer-1. Correct? A: It included everything. Yeah.").) The Court should reject Teva's attempts to paint the literature process described by Dr. Iyer and Dr. Bishop as one based solely on the patents-in-suit.

Regardless of the content of this 2005 presentation, the focus of the Court's infringement inquiry must be on the process used to manufacture the product that will eventually be marketed by Sandoz. Moreover, Dr. Iyer's use of the patent in his initial studies on how to manufacture copolymer-1 is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra*.

296. Steve Brugger, Vice-President of Strategic Product Development for Momenta acknowledged in a presentation given to Sandoz that there were "[m]ultiple opportunities for development of alternate process." (PTX 119 at MMT01078913; PTX 957 (Brugger Dep.) at 74:19-75:10.)

Sandoz's Response:

Dr. Brugger presented a slide containing this phrase as part of a presentation of almost 60 slides in 2005. (PTX 119 at MMT01078867, PTX 957 (Brugger Dep.) at 75:4-10.) The fact that this slide mentions the possibility of alternate processes does not mean that Mr. Brugger "acknowledged" this statement. It is unremarkable that, like any pharmaceutical company attempting to manufacture a generic drug, Sandoz would try to produce an equivalent glatiramer acetate product without infringing the Orange Book patents. Further, what was presented by Dr. Brugger in 2005 is inconsequential to the question of infringement, which must focus on the

process and product that will eventually be marketed upon approval. Momenta's development efforts are protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra*.

297. Dr. Iyer's team worked on replicating the patented "literature process." (PTX 960 (Iyer Dep.) at 32:7-19, 32:21-22, 32:23-25.) At the same time, Momenta contracted out work on developing a "non-literature process." (PTX 960 (Iyer Dep.) at 32:7-19, 32:21-22, 32:23-25, 33:16-34:8.)

Sandoz's Response:

As discussed above in Sandoz's Response to ¶¶ 294-5, the so-called "literature process" as described by Momenta was not based solely on the Teva patents, but instead drew from the vast amount of literature available regarding Copaxone, including its label and insert, scholarly publications, and multiple patents and patent applications, including both the '550 patent and the Gad patents. Teva claims that Dr. Iyer described the "literature process" as "patented," but none of its citations to his deposition support this assertion. (PTX 960 (Iyer Dep.) at 32:7-19, 32:21-22, 32:23-25.) In fact, Dr. Iyer repeatedly corrects attempts to paint the "literature process" as patented, or based solely on Teva's patents. (*See, e.g.,* PTX0960 (Iyer Dep.) at 130:7-9, 11, 46:20-47:9.)

Dr. Iyer's use of the patent in his initial studies on how to manufacture copolymer-1 is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.* Moreover, Momenta's early efforts to determine the proper process for manufacturing its proposed product are irrelevant, as the Court's focus must be on the product that will eventually marketed by Sandoz, and the process used to manufacture that product.

298. Momenta also did its own experimental work on an alternative non-literature process, and eventually filed a patent application on alternative routes for making copolymer-1. (PTX 177; PTX 785; PTX 960 (Iyer Dep.) at 159:24-160:18.)

Sandoz's Response:

The phrase "alternative non-literature process" is so vague as to prevent Sandoz from fully responding to this proposed finding, and should prevent the Court from adopting it. Teva once again tries to move the Court's focus to Sandoz and Momenta's early activities directed at development of a generic Copaxone product, when the only inquiry is the process Sandoz and Momenta will employ to create the product that will eventually be marketed. It is unremarkable that, like any pharmaceutical company attempting to manufacture a generic drug, Sandoz would try to produce an equivalent glatiramer acetate product without infringing the Orange Book patents. Moreover, Momenta's use of the patent in its early studies on how to manufacture copolymer-1 is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

299. Momenta stopped working on an alternative process in 2007, and decided to go forward with filing its ANDA using Teva's patented process. (PTX 960 (Iyer Dep.) at 37:7-10, 41:6-13, 113:16-19, 127:24-128:3, 130:7-17, 138:5-13; PTX 957 (Brugger Dep.) at 78:16-79:23.)

Sandoz's Response:

Momenta's use of the patented process in its efforts to file an ANDA and bring a generic glatiramer acetate product to market is a classic example of the kind of conduct protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.* It is therefore irrelevant to the infringement inquiry.

Moreover, Teva misstates Dr. Iyer's testimony. When asked if the "literature process" ultimately became the ANDA process, Dr. Iyer responded that the literature process, which derived from the vast literature on Copaxone, and not solely on Teva's patents, actually "evolved into" the ANDA process. (PTX 960 (Iyer Dep.) 138:10-13.) Teva's implication that Sandoz's ANDA process was identical to Teva's patented process is therefore misleading. Finally,

Sandoz's process for manufacturing its glatiramer acetate product contained in its original ANDA is irrelevant to the infringement inquiry, as that process has changed and will not be used by Sandoz to manufacture the product that will be marketed upon approval.

300. A May 2007 internal Momenta presentation explained Momenta's reasoning for abandoning the development of an alternative, non-infringing process. Momenta decided to file its ANDA using Teva's patented process because it "[e]nable[d] a first-to-file approach" and "[m]itigate[d] risk regarding chemical equivalence." (PTX 172 at MMT01287394.) In other words, as Dr. Iyer explained, Momenta decided to copy Teva's patented process for making copolymer-1 instead of developing its own process because it provided the quickest route to a regulatory filing. (PTX 960 (Iyer Dep.) at 127:18-128:3.) Dr. Iyer further testified that the time of 17 hours and a temperature of 26 degrees used in Step 2 of his process, the debenzylation step, was copied out of Teva's patent. (PTX 960 (Iyer Dep.) at 147:17-25, 148:3-7, 148:9-11.)

<u>*Sandoz's Response:*</u>

When Momenta's John Bishop was asked live at trial about Momenta's reasoning [redacted] for choosing different options for its current process and product, Teva repeatedly objected that the testimony was irrelevant. (*E.g.*, Sept. Tr. 1100:8-21; 1101:17-20.) Now, Teva is trying to use deposition designations about Momenta's reasoning in 2007 to show that Sandoz's current product infringes. The Court should not exclude Dr. Bishops live testimony on the subject but consider the deposition designations for the same area of testimony.

Regardless, the testimony about the old process does not support a finding of infringement. Teva misconstrues the deposition testimony of the Momenta witnesses in order to argue that Momenta's process was based entirely on Teva's patents, and not on any of the other literature available about Copaxone, which Dr. Bishop, Dr. Iyer, and Mr. Brugger all testified contributed to the development of the ANDA process. Specifically, Teva's assertion that Dr. Iyer "decided to copy Teva's patented process," finds no support in the record, as Dr. Iyer repeatedly testified that the literature process selected was based on all of the available literature about Copaxone, and not just Teva's patents. (*See, e.g.,* PTX0960 (Iyer Dep.) at 130:7-9, 11, 46:20-47:9.)

Teva also cites to a Momenta Technical Plan, claiming that Momenta "abandoned" an alternative process for developing its proposed glatiramer acetate product in favor of the literature process. But that document, while explaining that Momenta has chosen to prioritize the "literature route," specifically keeps open the option of a "novel route," also called "Strategy #1": "Strategy # 1 will be coprocessed post-filing. If this novel route is assessed as having benefits such as decreasing the time to launch, this team may re-evaluate the novel route's priority." (PTX 172 at MMT01287393-94.) As the technical plan makes clear, Sandoz and Momenta had not "abandoned" the possibility of developing a "novel route" for manufacturing a generic Copaxone product. And regardless of the process originally contained in Sandoz's ANDA, the focus of the infringement inquiry must be on the process Sandoz will use to produce the product to eventually be marketed.

The issue of copying is a red herring because Sandoz's current process for its Step 2 debenzylation process calls for a temperature of [redacted] and does not use time as a factor. (PTX 913-R at 37.) Further, Momenta's use of the patented process in its efforts to file an ANDA and bring a generic glatiramer acetate product to market is a classic example of the kind of conduct protected under the safe harbor provision of 271(e). It is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

(b) Original ANDA Process

Sandoz's Response:

Sandoz generally disputes the infringement analysis performed by Teva in paragraphs 301-311. Teva focuses on processes used by Sandoz and Momenta that have been abandoned, likely because Teva understands that the current process, which will be used to manufacture the product eventually marketed by Sandoz, does not infringe. But, as the Federal Circuit has recognized, an infringement inquiry under 35 U.S.C. § 271(e)(2)(A) requires a comparison of the

claims of the asserted patents against the product that is likely to be sold following FDA approval. *See Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002).

Thus, Sandoz's process as described in its original ANDA is not the proper focus of the Court's inquiry, which must examine the product that will eventually be marketed in determining infringement.

301. Sandoz's ANDA section 3.2.S.2.2, entitled "Description of Manufacturing Process and Process Controls (Glatiramer Acetate)," sets forth the details of Sandoz's manufacturing process for its proposed product. (Sept. Tr. (Gokel) 356:2-15; PTX 216 at SDZ00001937.) [redacted]

Sandoz's Response:

Teva's characterization of Sandoz's "basic synthetic process" for its proposed product is misleading. As discussed above, and as confirmed by Drs. Bishop and Laird, Sandoz has revised its process for manufacturing glatiramer acetate, and will follow that revised process in manufacturing all future batches. (Sept. Tr. 1099:21-23; 1100:25-1101:3; 1103:24-1104:7 (Bishop); PTX 913R.)

302. Broadly speaking, Sandoz uses the same four-step patent process to make its glatiramer acetate active ingredient that Mylan uses.

Sandoz's Response:

Although Mylan's and Sandoz's processes result in glatiramer acetate with substantially similar molar ratios, the process for manufacturing Sandoz's proposed product differs from Mylan's process in that Sandoz uses an in-process viscometry method to determine the endpoint of its Step 2 depolymerization reaction. (Sept. Tr. 1099:21-23; 1100:25-1101:3; 1103:24-1104:7 (Bishop); PTX 913R.) There may be other differences between Mylan's and Sandoz's processes, and each process must be evaluated separately by the Court in its infringement analysis. Moreover, the relevant inquiry is whether Sandoz's proposed manufacturing process

meets each and every limitation of the asserted *claims*, and not Teva's interpretation of the "patent process."

303. In Step 1, as in the patent process, Sandoz combines the N-carboxyanhydrides of alanine, benzyl protected glutamic acid, TFA protected lysine and tyrosine with the initiator diethylamine to form protected copolymer-1, which Sandoz calls Intermediate-1. (Sept. Tr. (Gokel) 348:13-22, 357:2-359:11; PTX 216 at SDZ00001937-38.)

Sandoz's Response:

The claims at issue describe the process exactly as Teva recites it in No. 303. The relevant inquiry is whether Sandoz's proposed manufacturing process meets each and every limitation of the asserted *claims*, and not Teva's interpretation of the "patent process."

304. In Step 2, as in the patent process, Intermediate-1 is reacted with HBr/acetic to form TFA protected copolymer-1, which Sandoz calls Intermediate-2. (Sept. Tr. (Gokel) 359:5-11, 368:4-8; PTX 216 at SDZ00001937-38.)

Sandoz's Response:

The claims at issue describe the process exactly as Teva recites it in No. 304. The relevant inquiry is whether Sandoz's proposed manufacturing process meets each and every limitation of the asserted *claims*, and not Teva's interpretation of the "patent process." Sandoz does not dispute the content of its original ANDA, but it is irrelevant to the infringement inquiry, as Sandoz no longer employs the Step 2 depolymerization process described in its original ANDA to manufacture its glatiramer acetate product. (Sept. Tr. 1105:1-8 (Bishop).) Sandoz's original ANDA that contains steps no longer used for manufacturing its proposed product is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

305. As in the patent process, the time and temperature of the Step 2 reaction is used to control the molecular weight of Sandoz's product and ensure that it meets the specification of 5,000 to 9,000 daltons. (Sept. Tr. (Gokel) 361:20-363:13; Sept. Tr. (Sampson) 1641:18-1642:8; PTX 213; PTX 214 at SDZ00000186.)

Sandoz's Response:

The relevant inquiry is whether Sandoz's proposed manufacturing process meets each and every limitation of the asserted *claims*, and not Teva's interpretation of the "patent process." Sandoz does not dispute the content of its original ANDA, but it is irrelevant to the infringement inquiry, as Sandoz no longer employs the Step 2 depolymerization process described in its original ANDA to manufacture its glatiramer acetate product. (Sept. Tr. 1105:1-8 (Bishop).) Sandoz's original ANDA that contains steps no longer used for manufacturing its proposed product is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.* In Sandoz's current Step 2 process, time is not used to control the molecular weight of Sandoz's product. The endpoint of the reaction is determined by a viscometry method, which does not measure time, but instead measures viscosity, a physical feature of the solution. *See* Section (d), *infra.*

306. Sandoz determined the target time and temperature for Step 2 using "profile runs." (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.)

Sandoz's Response:

Sandoz does not dispute the content of its original ANDA which describes the use of large scale profile runs, but it is irrelevant to the infringement inquiry, as Sandoz no longer employs the large scale profile runs described in its original ANDA to manufacture its glatiramer acetate product. Momenta and Sandoz's use of the large scale profile runs described in its original ANDA to bring a generic glatiramer acetate product to market is a classic example of the kind of conduct protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.* It is therefore irrelevant to the infringement inquiry.

307. During these profile runs, samples of Intermediate-1 were taken at varying times during the Step 2 HBr/acetic acid reaction. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.) The samples were then subjected to Steps 3 and 4 of Sandoz's manufacturing process and converted to glatiramer acetate. The average molecular weights of the resulting

batches of glatiramer acetate were determined. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.)

<u>*Sandoz's Response:*</u>

Sandoz does not dispute the content of its original ANDA describing large scale profile runs, but it is irrelevant to the infringement inquiry, as Sandoz no longer employs the large scale profile runs described in its original ANDA to manufacture its glatiramer acetate product. Momenta and Sandoz's use of the large scale profile runs described in its original ANDA to bring a generic glatiramer acetate product to market is a classic example of the kind of conduct protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.* It is therefore irrelevant to the infringement inquiry.

308. With this data, Sandoz was able to determine the window of time for the Step 2 reaction that would allow Sandoz to obtain a glatiramer acetate having an average molecular weight between 5,000 and 9,000 daltons. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.)

<u>*Sandoz's Response:*</u>

Sandoz does not dispute the content of its original ANDA, but it is irrelevant to the infringement inquiry, as Sandoz no longer employs the Step 2 reaction and large scale profile runs as described in its original ANDA to manufacture its glatiramer acetate product. Momenta and Sandoz's use of the large scale profile runs described in its original ANDA to bring a generic glatiramer acetate product to market is a classic example of the kind of conduct protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.* It is therefore irrelevant to the infringement inquiry.

309. The reaction conditions of time and temperature determined from the profile runs were applied to Sandoz's production batches. (Sept. Tr. (Gokel) 424:12-425:15; Sept. Tr. (Bishop) 1098:16-1099:6; PTX 214 at SDZ00000186.) [redacted]

Sandoz's Response:

Sandoz does not dispute the content of its original ANDA, but it is irrelevant to the infringement inquiry, as Sandoz no longer employs the Step 2 reaction and large scale profile runs as described in its original ANDA [redacted] to manufacture its glatiramer acetate product. Momenta and Sandoz's use of the large scale profile runs described in its original ANDA, and its use of a Step 2 reaction that is run for 43-47 hours at a temperature of 20 ± 2°C are classic examples of the kind of conduct protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.* It is therefore irrelevant to the infringement inquiry. In Sandoz's current Step 2 process, time is not used to control the molecular weight of Sandoz's product. The endpoint of the reaction is determined by a viscometry method, which does not measure time, but instead measures viscosity, a physical feature of the solution. *See* Sandoz's Response to ¶¶ 312-325, *infra.*

310. In Step 3 of the Sandoz and patent processes, Intermediate-2 is treated with piperidine, which removes the TFA protecting groups from the lysines. (Sept. Tr. (Gokel) 359:17-360:9, 368:9-13; PTX 216 at SDZ00001937-38.) The resulting product is referred to in Sandoz's ANDA as Intermediate-3.

Sandoz's Response:

The relevant inquiry is whether Sandoz's proposed manufacturing process meets each and every limitation of the asserted *claims*, and not Teva's interpretation of the "patent process."

311. In Step 4, the final step of both the Sandoz and patent processes, Intermediate-3 is purified by a step called diafiltration. During this step, acetic acid is used. (Sept. Tr. (Gokel) 360:3-18, 361:3-19; PTX 216 at SDZ00001937-38, 949.) The product of Step 4 is glatiramer acetate, or copolymer-1. (Sept. Tr. (Gokel) 360:3-18; PTX 216 at SDZ00001937-38.)

Sandoz's Response:

The relevant inquiry is whether Sandoz's proposed manufacturing process meets each and every limitation of the asserted *claims*, and not Teva's interpretation of the "patent process."

(c) Briefing Book

312. [redacted]

Sandoz's Response:

Sandoz's in-process viscosity control was considered by Momenta starting at least as early as 2008 [redacted] (*See* Sandoz's Letter to the Court Regarding Teva's Request for Additional Discovery, Aug. 16, 2011, at 2.) [redacted] Sandoz confirmed to the FDA that this in process-control had been implemented:

> Q. And did you also inform the FDA that you were no longer going to be using 1.0[.]0 process or the process that was used of 1.0.0?
>
> A. Yes, we informed the FDA that we were moving to this revised process designated 1.1.0.
>
> Q. And has Momenta abandoned the process that it used in 1.0[.]0 for determining the depolymerization end point?
>
> A. Yes, we have.

(Sept. Tr. 1105:1-8 (Bishop).)

The Briefing Book is a formal communication to the FDA, and Dr. Bishop confirmed that, moving forward, Sandoz will use this new viscosity test, which eliminates profile runs or engineering runs (the step Teva's experts claimed was a "test reaction") from its manufacturing process. (*See* Sept. Tr. 1105:9-11 (Bishop).)

313. The Briefing Book discusses using an in-process control based on viscosity to determine the endpoint of the Step 2 HBr/acetic acid reaction. (Sept. Tr. (Gokel) 426:3-427:6; PTX 913 at 36.) Viscosity is a property that describes the fluidity of a solution. (Sept. Tr. (Gokel) 427:7-11.) For example, gasoline or water have a low viscosity, whereas honey has a high viscosity. (Sept. Tr. (Gokel) 427:7-11.)

Sandoz's Response:

Undisputed.

314. The Briefing Book does not provide details of the proposed viscosity in-process control method. The batch records for Sandoz's lots of glatiramer acetate, however, contain some additional information on the possible method. (PTX 928 at MMT01707032-040.)

Sandoz's Response:

The Briefing Book contained the basic details about the viscosity in-process control, including an outline of the process, initial validation data, and a description of the advantages of the viscosity test as opposed to previous methods. (*See* PTX 913 at 36-39.) The in-process control was further discussed with the FDA [redacted]

315. According to the batch records there are actually two alternative methods for determining the endpoint of Step 2. (Sept. Tr. (Gokel) 430:7-25; PTX 914 at MMT01630951.)

Sandoz's Response:

Although the batch records formerly described an alternative, or "backup" method using a time and temperature correlation, that method is no longer employed by Momenta. Momenta will use its in-process viscosity method going forward, using a backup viscometer as an alternative in the event the primary viscometer fails:

> Q. And is there another back up to the viscometer that you have been talking about up till now?
>
> A. Yes. We have a back up viscometer which now serves as the back up to the main viscometer.
>
> . . . .
>
> Q. And does Momenta intend to use viscometer, I'll call it viscometer number two, in its product going forward?
>
> A. That will be our back up to the main viscometer, yes.

(Sept. Tr. 1106:4-7, 12-14 (Bishop).)

Sandoz does not dispute the content of its batch records describing a time and temperature correlation, but it is irrelevant to the infringement inquiry, as this method is no longer used by Sandoz. (Sept. Tr. 1105:1-8 (Bishop).) Sandoz's proposed use of this method is a classic example of the kind of conduct protected under the safe harbor provision of 271(e). See Sandoz's Response to Section VI.B.ii.2.a, supra. It is therefore irrelevant to the infringement inquiry.

316. The first alternative is the in-process control referred to in the Briefing Book, which Sandoz calls the "viscometer model." (Sept. Tr. (Gokel) 430:7-436:23; PTX 914 at MMT01630951-955; PTX 928 at MMT01707035.)

Sandoz's Response:

As discussed above, the use of a primary viscometer, along with a backup viscometer to provide measurements in the event of a failure, is the only method Sandoz employs for its Step 2 reaction. (*See* Sept. Tr. 1105:1-8 (Bishop).)

317. The premise of the viscometer model is that the viscosity of an Intermediate-1 sample at a given temperature can be correlated with the average molecular weight of the final glatiramer acetate product. (Sept. Tr. (Gokel) 426:3-427:6; PTX 913 at 36.) According to Sandoz's proposed method, the Step 2 HBr/acetic acid reaction would be stopped when a viscosity was reached that would provide a final glatiramer acetate product having the targeted average molecular weight of [redacted] daltons. (Sept. Tr. (Gokel) 432:11-23; PTX 914 at MMT01630953.)

Sandoz's Response:

Sandoz does not dispute that viscosity of the step 2 solution at particular temperatures can be correlated with the target molecular weight of the final glatiramer acetate product, but objects to Teva's description as misleading. The idea that viscosity can be correlated with the molecular weight of the final copolymer-1 product is not a "premise," it is an actual correlation observed by Momenta scientists. The reliability of this correlation and the "robustness" of the in-process control led Sandoz and Momenta to implement the viscosity method for all future lots of its glatiramer acetate product. (Sept. Tr. 1105:22-1106:14 (Bishop); PTX 913 at 36.)

318. The Intermediate-1 viscosity values that would give glatiramer acetate final product having the targeted average molecular weight of [redacted] daltons were previously determined by Sandoz using test reactions. In these test reactions, samples of Intermediate-1 were reacted with HBr/acetic acid at varying times and temperatures, and the viscosity values were measured. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-114.) The samples of Intermediate-1 were then converted to glatiramer acetate, and the average molecular weights of the glatiramer acetate samples were determined. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-114.)

Sandoz's Response:

Sandoz maintains that its proposed construction of the "predetermined by test reaction" limitation is the correct one. Regardless, the testing of samples of the step 2 solution cited by Teva does not predetermine *both* the time and temperature to react protected copolymer-1 with HBr/acetic acid. (Sept. Tr. 1134:25-1135:8, 1137:6-1138:7 (Laird).) If it did, there would be no need for the viscosity in-process control. Moreover, the testing of prior batches for purposes of regulatory approval is immune under 35 U.S.C. § 271(e)(1) (2006). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

319. Using this data, Sandoz determined what viscosity value of Intermediate-1 at a given temperature would result in final glatiramer acetate product having an average molecular weight of [redacted] daltons. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-114.)

Sandoz's Response:

Sandoz determined what viscosity value of the step 2 solution at a given temperature would result in a final glatiramer acetate product having a molar mass (Mp) of [redacted] daltons. (PTX 914R.) Sandoz maintains that its proposed construction of the "predetermined by test reaction" limitation is the correct one. Regardless, the testing of samples cited by Teva does not predetermine *both* the time and temperature to react protected copolymer-1 with hydrobromic acid. (Sept. Tr. 1134:25-1135:8, 1137:6-1138:7 (Laird).) If it did, there would be no need for the viscosity in-process control. Moreover, the testing of prior batches for purposes of regulatory

approval is immune under 35 U.S.C. § 271(e)(1) (2006). It is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

320. Sandoz took the viscosity and temperature information it obtained and created a table of predetermined targeted viscosity values for given reaction temperatures. (Sept. Tr. (Gokel) 436:18-439:6; PTX 928 at MMT01707035.) The table contains temperatures ranging [redacted] (Sept. Tr. (Laird) 1159:19-1160:3; PTX 928 at MMT01707035.) The Step 2 reaction is stopped when the targeted viscosity value is reached for the Step 2 reaction temperature. (Sept. Tr. (Gokel) 430:17-431:24; PTX 914 at MMT01630952-953; PTX 928 at MMT01707035.)

<u>*Sandoz's Response:*</u>

Teva uses the word "predetermined" in this finding in order to imply that Sandoz's table of viscosity and temperature correlations satisfies the "predetermined by test reaction" claim limitation. However, Teva must show that Sandoz uses *both* a time and temperature predetermined by test reaction in order to meet its burden on this claim limitation.

321. Momenta documents indicate that as time increases, the viscosity decreases. (PTX 914 at MMT01630951-53.) Thus, the longer Intermediate-1 reacts with HBr/acetic acid, the lower its viscosity. This enables Sandoz to use viscosity, which changes as a function of time, rather than time itself to monitor the progress of the reaction and determine when to stop it in order to obtain a glatiramer acetate having an average molecular weight of [redacted] daltons. (Sept. Tr. (Gokel) 430:7-16, 434:9-17.)

<u>*Sandoz's Response:*</u>

Although viscosity decreases over time, this correlation cannot provide an actual *endpoint* at which to stop the reaction in order to ensure that the operator has obtained a glatiramer acetate having the target molecular weight. As Momenta's batch records explain, "[v]iscosity is a macroscopic parameter and is dependent on multiple process variables, including molecular weight, temperature, and concentration." (PTX 914 at MMT01630951.) Therefore, there are several factors that will influence how long it will take for a certain viscosity to be reached. (*Id.*) Armed only with the knowledge that viscosity "changes as a function of

time," the operator could not determine the appropriate endpoint of the reaction. Dr. Gokel admitted as much:

> Q. Yes, but my question is, talking about the operator, running the reaction, and you agree with me that the operator cannot just set this alarm clock that you mentioned and leave for 30 hours and come back with complete certainty that the viscosity level associated with a particular temperature has been reached, can she?
>
> A. Not with complete certainty.

(Sept. Tr. 519:19-25.) Sandoz's Briefing Book also bears this out, listing the duration of the Step 2 reaction as "N/A." (PTX 913.)

322. The second alternative method for determining the endpoint of the Step 2 reaction described in Sandoz's batch records is a "time and temperature model." It is to be used "[i]n the event of the viscometer equipment failure or the inability to obtain accurate viscosity readings . . . ." (Sept. Tr. (Laird) 1160:20-25; PTX 928 at MMT01707035-036.) Like the viscometer model, the "time and temperature model" utilizes a table with temperatures ranging from redacted , but time, rather than viscosity, at a given temperature is used to determine when to stop the HBr/acetic acid reaction in order to achieve a final glatiramer acetate product having an average molecular weight of [redacted] daltons. (PTX 928 at MMT01707036.)

Sandoz's Response:

As discussed above, the use of a primary viscometer, along with a backup viscometer to provide measurements in the event of a failure, is the only method Sandoz employs for its Step 2 reaction. The method described above is no longer used by Sandoz. (Sept. Tr. 1105:1-8 (Bishop).) Moreover, Sandoz's prior investigation on how to manufacture copolymer-1 is protected under the safe harbor provision of 35 U.S.C. § 271(e)(1) (2006). It is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

323. The time and temperature values in the table are based on results of prior test reactions. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 115-124.) In these test reactions, samples of Intermediate-1 were reacted with HBr/acetic acid at varying times and temperatures. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 115-124.) The samples of Intermediate-1 were then converted into glatiramer acetate, and the average molecular weight of the samples of glatiramer acetate were determined. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 115-124.)

Sandoz's Response:

As discussed above, the use of a primary viscometer, along with a backup viscometer to provide measurements in the event of a failure, is the only method Sandoz employs for its Step 2 reaction. The method described above is no longer used by Sandoz. (Sept. Tr. 1105:1-8 (Bishop).) Moreover, Sandoz's prior investigation on how to manufacture copolymer-1 is protected under the safe harbor provision of 35 U.S.C. § 271(e)(1) (2006) and is irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

324. Using this data, Sandoz determined how time and temperature correlated with a final glatiramer acetate product having an average molecular weight of [redacted] daltons. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 115-124.) This information was used to create the time and temperature table. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 115-124.)

Sandoz's Response:

As discussed above, the use of a primary viscometer, along with a backup viscometer to provide measurements in the event of a failure, is the only method Sandoz employs for its Step 2 reaction. The method described above is no longer used by Sandoz. (Sept. Tr. 1105:1-8 (Bishop).) Moreover, Sandoz's prior investigation on how to manufacture copolymer-1 is protected under the safe harbor provision of 35 U.S.C. § 271(e)(1) (2006), and is irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

325. As explained above, the current batch records set forth both a viscometer model and a time and temperature model. (Sept. Tr. (Laird) 1158:17-18, 1163:2-4; PTX 928 at MMT01707035-036.) If Sandoz submits to the FDA any future amendments to its ANDA, it must submit the underlying batch records. (Sept. Tr. (Laird) 1157:11-14.) Thus, the FDA would receive batch records containing both the viscometer model and the time and temperature model.

Sandoz's Response:

Dr. Bishop testified that Momenta's future records will be revised to remove the back-up time-temperature model:

> Well, we are updating our records to -- we successfully used viscosity during our process validation campaign earlier this year, and so we have this back up in the event that viscometry failed during those process validation runs, since it didn't fail, and we have confidence now in our ability to use viscometry as an in process control, we no longer need this methodology as a back up, and we will be taking that out of our process henceforth.

(Sept Tr. 1108:19-1109:1.)

[redacted]

Momenta and Sandoz's proposed (and discontinued) use of this model to bring a generic glatiramer acetate product to market is a classic example of the kind of conduct protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.* It is therefore irrelevant to the infringement inquiry.

Teva improperly cites the testimony of British process chemist Dr. Trevor Laird, who did not provide opinions as an expert in regulatory compliance, the ANDA process or communications with the FDA.

(3) <u>Sandoz's ANDA Product Label</u>

326. The proposed label for Sandoz's ANDA product has the identical indication and dosage information as in Teva's Copaxone® label. (Sept. Tr. (Lisak) 141:13-145:6; PTX 206 at SDZ00000034, 044; PTX 697.) Sandoz's proposed product label states that the product is "indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis." (Sept. Tr. (Lisak) 141:13-145:6; PTX 206 at SDZ00000034.) If Sandoz's ANDA product was approved by the FDA, its use would comprise a method of treating multiple sclerosis (Sept. Tr. (Lisak) at 145:21-146:1, 146:23-147:1), and Sandoz's proposed label would encourage physicians to use the ANDA product to treat patients with multiple sclerosis. (Sept. Tr. (Lisak) 147:16-19.)

<u>*Sandoz's Response:*</u>

Unremarkably, and as required by 21 U.S.C. § 355(j)(2)(A)(v), Sandoz's label for its proposed product mirrors that of the reference listed drug, Copaxone.

C. Sandoz's Responses to Teva's Proposed Conclusions of Law on Infringement.

(i) Teva Has Not Proven that Sandoz's Proposed Product Infringes Each of the Asserted Claims

390. The Plaintiffs presented evidence at trial that Sandoz's proposed product meets each and every limitation of the asserted claims. (Sept. Tr. (Gokel) 413:22-415:15, 447:20-469:7; PTX 987 at 101-110.) Sandoz has contested infringement of only two claim limitations: copolymer-1 and test reaction. For the reasons set forth below, Sandoz's proposed product infringes each of the asserted claims.

Sandoz's Response:

Teva has the burden to prove that each and every limitation of the asserted claims is met by Sandoz's proposed product. *Mas-Hamilton Grp. v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998). The fact that Sandoz may not have "contested" a limitation does not absolve Teva of its duty to present evidence to satisfy its burden on that limitation. As explained in Sandoz's Findings of Fact and Conclusions of Law ¶¶ 1-39 and as described below, Teva cannot prove that Sandoz's proposed product meets each and every limitation of the asserted claims.

D. Sandoz's Product Does Not Infringe the Asserted Claims.

(i) Sandoz's Product is Not Copolymer-1

391. From the beginning of this litigation up until almost the eve of trial, Sandoz did not dispute that its proposed generic Copaxone® product was copolymer-1. In its pretrial submissions, however, Sandoz raised for the first time an argument that its proposed product is not copolymer-1 because it does not have an amino acid molar ratio of approximately 6:2:5:1. Sandoz's argument is without merit.

Sandoz's Response:

Starting with its answer to the complaint, Sandoz denied that it infringed the patents. (Answer, at ¶¶ 35-66.) Sandoz has repeatedly told both Teva and the Court that it does not infringe the patents-in-suit. (*E.g.*, Feb. 10, 2010 Reply ISO MSJ, at 1.) Teva has the burden of proof to show that Sandoz's product meets the definition of copolymer-1 by a preponderance of

the evidence. Sandoz is entitled to present evidence to rebut Teva's allegations that its proposed product meets each and every limitation of the asserted claims.

392. As set forth above, Sandoz's ANDA provides molar fraction data for its proposed product. As Dr. Gokel testified at trial, and as can be seen in Figure 18 below, when Sandoz's molar fraction data and "6:2:5:1" are compared on the same scale, it is plain that Sandoz's molar ratio is approximately 6:2:5:1. (Sept. Tr. (Gokel) 417:14-421:16; PTX 987 at 90.) Dr. Gokel's testimony was unrebutted.

<u>Figure 18</u>

Sandoz Original ANDA Lot 077K7277

Amino Acid	6:2:5:1	6:2:5:1 (Scale = 1)	Lot 077K7277 (Scale = 1)		Scale = 14	
A	6	.43	.436	x 14	6.10	6
G	2	.14	.147	x 14	2.06	2
L	5	.36	.334	x 14	4.68	5
T	1	.07	.083	x 14	1.16	1
Scale	14	1	1		14	14

90

<u>Sandoz's Response:</u>

This testimony was not rebutted because the molar ratios in Sandoz's original ANDA do not reflect the molar ratio of the product that will ultimately be marketed by Sandoz. Sandoz's development efforts and products described in its original ANDA are a classic example of the kind of conduct protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra*. It is therefore irrelevant to the infringement inquiry. Sandoz's most recent batches, produced using the process that will be used to manufacture all future batches, have different molar ratios than those in Sandoz's original ANDA. (Sept. Tr. 1093:17-1094:3 (Bishop).); PTX 913-R, at 28, Table 6.) As the Federal Circuit has recognized, "the focus of the

infringement inquiry under 35 U.S.C. § 271(e)(2)(A) is on the product that will be sold after the FDA's approval of the ANDA…not on the biobatch that is produced to facilitate FDA approval." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1249 (Fed. Cir. 2000) (citation omitted); *see* Sandoz's Response to Section VI.B.ii.2.a, *supra*.

393. Contrary to what Sandoz has argued, [redacted] is considered (even though Sandoz has not yet amended its ANDA to include the man uring process that results in these molar fractions). As Dr. Gokel testified, and as can be seen in Figure 19 below, the molar ratio in Sandoz's new lot is also approximately 6:2:5:1. (Sept. Tr. (Gokel) 420:3-422:15; PTX 987 at 95.) This testimony was also unrebutted.

<u>Figure 19</u>

Sandoz New Lot 051M7282

Amino Acid	6:2:5:1	6:2:5:1 (Scale = 1)	Lot 051M7282 (Scale = 1)		Scale = 14	
A	6	.43	.427	x 14	5.98	6
G	2	.14	.136	x 14	1.90	2
L	5	.36	.344	x 14	4.82	5
T	1	.07	.093	x 14	1.30	1
Scale	14	1	1		14	14

95

<u>Sandoz's Response:</u>

Teva's assertion that Sandoz's most recent batches of its proposed product contain a molar ratio of approximately 6:2:5:1 is without merit. As shown in Figure 19, even on Teva's "scale of 14," Sandoz's proposed product contains 30% more tyrosine (a difference of 1 to 1.3 tyrosines). (*See* Sept. Tr. 491:16-492:6 (Gokel); 715:3-8, 777:4-15 (Kent).)

Sandoz further incorporates Mylan's Opposition to Teva's Proposed Findings of Fact and Conclusions of Law regarding molar ratio, including Dr. Gokel's method of calculating the molar ratio of Mylan's and Sandoz's proposed products.

394. Sandoz's proposed product therefore literally meets the limitation of "approximately 6:2:5:1" and is copolymer-1 within the meaning of the asserted claims.

Sandoz's Response:

As discussed above and in Sandoz's Proposed Findings of Fact and Conclusions of Law ¶¶ 14-18 and 39, Sandoz's proposed product does not meet this limitation, as it contains 30% more tyrosine than a copolymer-1 with a molar ratio of approximately 6:2:5:1. (*See* Sept. Tr. 491:16-492:6 (Gokel); 715:3-8, 777:4-15 (Kent).)

Sandoz further incorporates Mylan's Opposition to Teva's Proposed Findings of Fact and Conclusions of Law regarding molar ratio.

395. Even if Sandoz's product did not literally meet the requirement of a molar ratio of "approximately 6:2:5:1," it would meet that requirement under the doctrine of equivalents.

Sandoz's Response:

Sandoz's product, with over 30% more tyrosine than the claimed molar ratio, is substantially different from copolymer having a molar ratio of "approximately 6:2:5:1." *See* Sandoz's Opening FFCOL Nos. 14-18, 39.

Sandoz further incorporates Mylan's Opposition to Teva's Proposed Findings of Fact and Conclusions of Law regarding molar ratio.

396. As shown in Figure 20 below, the percent total difference in amino acid ratios between Sandoz's product and exactly 6:2:5:1 is 4.4%. (Sept. Tr. (Sampson) 546:21-547:22; PTX 988 at 3.) For the reasons discussed above with respect to Mylan's product, Sandoz's proposed product is equivalent to approximately 6:2:5:1.

Figure 20

	Exactly "6:2:5:1"	Exactly "6:2:5:1" (expressed as %)	Sandoz's Molar Fraction	Expressed as %
A Alanine	.429	42.9%	.427	42.7%
G Glutamic Acid	.143	14.3%	.136	13.6%
L Lysine	.357	35.7%	.344	34.4%
T Tyrosine	.071	7.1%	.093	9.3%
Total	1	100%	1	100%
				4.4% total difference

Molar fraction data taken from PTX 913 at MMT01630061

Sandoz's Response:

Sandoz incorporates Mylan's Opposition to Teva's Proposed Findings of Fact and Conclusions of Law regarding molar ratio, particularly as it relates to Dr. Sampson's calculation of the "percent total difference" between the proposed product and a molar ratio of 6:2:5:1.

(ii) Sandoz's Product Does Not Meet the Molecular Weight Limitations

397. Dr. Grant explained at trial why Sandoz's ANDA product meets the molecular weight limitations of each of the asserted claims. (Sept. Tr. (Grant) 265:2-268:3.) Sandoz did not offer any testimony to rebut Dr. Grant's conclusions.

Sandoz's Response:

As discussed above in Sandoz's Response to ¶¶ 282-87, Sandoz's proposed product does not meet the molecular weight limitations of copolymer-1, in particular, because Sandoz's proposed product has a weight average molecular weight of greater than 10 kDa. (Sept. Tr. 1096:4-6 (Bishop); PTX 913-R at 53; PTX 349-R at SDZ00017953.) Further, Dr. Grant did not testify as to whether Sandoz's proposed product has a weight average molecular weight of less than 10 kDa. Thus, there was no need or opportunity for Sandoz to present any rebuttal.

(1) Average molecular weight limitations

398. Dr. Grant testified that Sandoz's method for determining the peak molecular weight values of its product involves using an appropriately calibrated suitable gel filtration column. (Sept. Tr. (Grant) 212:4-218:17; PTX 209 at SDZ00002017.)

Sandoz's Response:

As Sandoz stated in its claim construction papers, Sandoz respectfully submit that the correct claim construction should not include the ambiguous terms "appropriate" and "suitable." As discussed above in Sandoz's Response to ¶¶ 282-87, Sandoz's proposed product does not meet the molecular weight limitations of copolymer-1, in particular, because Sandoz's proposed product has a weight average molecular weight of greater than 10 kDa. (Sept. Tr. 1096:4-6 (Bishop); PTX 913-R at 53; PTX 349-R at SDZ00017953.) Dr. Grant gave no opinion as to whether Sandoz's proposed product has a weight average molecular weight of less than 10 kDa.

399. Based on Dr. Grant's testimony and the peak molecular weight data in Sandoz's ANDA, Sandoz's proposed product meets the molecular weight limitations of claims 1 of the '808 patent and claim 1 of the '589 patent, which require a copolymer-1 having an average molecular weight of "about 5 to 9 kilodaltons;" claims 1 and 6 of the '847 patent and claims 1, 8, 9, 12, 23, 30, and 31 of the '539 patent, which require a copolymer-1 having an average molecular weight of "about 4 to about 9 kilodaltons;" and claim 10 of the '539 patent, which requires a copolymer-1 with an average molecular weight of "6.25 to 8.4 kilodaltons." (Sept. Tr. (Grant) 223:20-225:2.)

Sandoz's Response:

As discussed above in Sandoz's Response to ¶¶ 282-87, Sandoz's proposed product does not meet the molecular weight limitations of copolymer-1, in particular, because Sandoz's proposed product has a weight average molecular weight of greater than 10 kDa. (Sept. Tr. 1096:4-6 (Bishop); PTX 913-R at 53; PTX 349-R at SDZ00017953.) Dr. Grant gave no opinion as to whether Sandoz's proposed product has a weight average molecular weight of less than 10 kDa.

(2) Copolymer-1 molar fraction limitations

400. Based on Dr. Grant's calculations, Sandoz's proposed product meets the molecular weight limitations of claims 1-3 of the '430 patent, which requires the copolymer-1 to have over 75% of its molar fraction within the molecular weight range of 2 and 20 kDa; claims 8 and 30 of the '539 patent, which require the copolymer-1 to have less than 2.5% of its molar fraction with molecular weights above 40 kDa; claims 9, 10, and 31 of the '539 patent and claim 8 of the '098 patent, which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 2.5% of its molar fraction with molecular weights greater than 40 kDa; claim 1 of the '476 patent, claim 1 of the '161 patent, and claim 1 of the '098 patent which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 5% of its molar fraction with molecular weights greater than 40 kDa. (Sept. Tr. (Grant) 233:23-235:2.)

Sandoz's Response:

As discussed above in Sandoz's Response to ¶¶ 282-87, Sandoz's proposed product does not meet the molecular weight limitations of copolymer-1. (Sept. Tr. 1096:4-6 (Bishop); PTX 913-R at 53; PTX 349-R at SDZ00017953.) Further, Dr. Grant did not testify as to whether Sandoz's proposed product has a weight average molecular weight of less than 10 kDa. Also, claim 3 of the '430 patent was not asserted against Sandoz.

(3) TFA copolymer-1 molar fraction limitations

401. Based on Dr. Grant's calculations, Sandoz's proposed product meets the molecular weight limitations of Claims 1-3 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent, which require that the TFA copolymer-1 that is made as a result of treatment of protected copolymer-1 with hydrobromic acid have over 75% of its molar fraction with molecular weights between 2 and 20 kDa. (Sept. Tr. (Grant) 239:11-240:8.)

Sandoz's Response:

As discussed above in Sandoz's Response to ¶¶ 282-87, Sandoz's proposed product does not meet the molecular weight limitations of copolymer-1. Further, Dr. Grant did not testify as to whether Sandoz's proposed product has a weight average molecular weight of less than 10 kDa. Also, claim 3 of the '430 patent was not asserted against Sandoz.

(iii) Sandoz's Process Does Not Meet the Process Limitations

402. With the exception of the "predetermined by test reaction" limitation, Sandoz has

not disputed that the manufacturing process in its ANDA meets the process limitations of the asserted claims.

Sandoz's Response:

Teva's characterization is both misleading and irrelevant. Sandoz has not addressed infringement in the context of its original ANDA manufacturing process, because that process is no longer employed by Sandoz, and will not be the process used to create the glatiramer acetate product that will eventually be brought to market. *See* Sandoz's Response to ¶ 23; *Abbott Labs. v. TorPharm, Inc*., 300 F.3d 1367, 1373 (Fed. Cir. 2002) (product that will eventually be marketed is subject of infringement inquiry). Sandoz's development steps in determining the manufacturing process to bring a generic glatiramer acetate product to market is a classic example of the kind of conduct protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.* It is therefore irrelevant to the infringement inquiry.

403. Based on Dr. Gokel's testimony and the information in Sandoz's ANDA, Sandoz's process meets the "reacting protected copolymer-1 with hydrobromic acid" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1-2 of the '898 patent, claims 1-2 of the '430 patent, claim 1 of the '476 patent and claim 1 of the '161 patent; the "treating trifluoroacetyl copolymer-1" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent; claims 1-3 of the '898 patent, claims 1-3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent and claims 1 and 6 of the '847 patent; the "purifying" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent and claims 1 and 6 of the '847 patent; the "selecting a predetermined molecular weight profile" limitation of claims 1-3 of the '898 patent; and the "copolymer-1 fraction" limitations of claim 1 of the '161 patent and claim 1 of the '476 patent. (Sept. Tr. (Gokel) 349:4-350:18, 354:16-363:13, 447:20-469:7.)

Sandoz's Response:

The process described in Sandoz's original ANDA is no longer employed by Sandoz, and will not be the process used to create the glatiramer acetate product that will eventually be brought to market. *See* Sandoz's Response to ¶ 23; *Abbott Labs*., 300 F.3d at 1373 (product that

will eventually be marketed is subject of infringement inquiry.) Also, claim 3 of the ’898 patent and claim 3 of the ’430 patent were not asserted against Sandoz.

(1) Sandoz’s Accused “Test Reaction”

404. Sandoz’s current ANDA, which comprises Sandoz’s original ANDA from 2007 [redacted] sets forth a process for making copolymer-1 in which test reactions are used to predetermine the time and temperature of the reaction of protected copolymer-1 with HBr/acetic acid. At trial, Sandoz did not contest that the manufacturing process, as set forth in the current ANDA, meets the “predetermined by test reaction” limitation in the asserted claims.

Sandoz’s Response:

Sandoz does not dispute the content of its original ANDA [redacted] but it is irrelevant to the infringement inquiry, as Sandoz no longer employs the process described in its original [redacted] to manufacture its glatiramer acetate product. *See* Sandoz’s Response to ¶¶ 23, 301-11; *Abbott Labs.*, 300 F.3d at 1373 (product that will eventually be marketed is subject of infringement inquiry.) Sandoz’s former Step 2 depolymerization process is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz’s Response to Section VI.B.ii.2.a, *supra*.

Sandoz’s current Step 2 depolymerization process, which uses an in-process viscometry control, does not meet the “predetermined by test reaction” limitation as it does not use a test reaction to predetermine the time required for the Step 2 process. (Sept. Tr. 1129:8-17 (Laird).) The FDA has been informed of this change in the manufacturing process. (Sept. Tr. 1105:1-11 (Bishop); PTX 913R.)

405. “Predetermined by a test reaction” has been construed to mean “determined beforehand by a reaction carried out to determine results of varying reaction conditions.” (D.I. 273, at 50.)

Sandoz's Response:

Sandoz maintains that its proposed construction of the "predetermined by test reaction" limitation is the correct one. But regardless of the construction of "predetermined by a test reaction," Sandoz's proposed process does not meet this limitation. The endpoint of Sandoz's current Step 2 depolymerization reaction is determined through the use of a viscometer, which does not measure time, but instead measures viscosity, a physical feature of the solution. (*See* Sandoz's Opening FFCOL Nos. 1-13, 34-37.) Sandoz's former Step 2 depolymerization process is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

406. According to the current ANDA, in order to obtain a copolymer-1 that would meet the average molecular weight specification of 5,000 to 9,000 daltons, Sandoz ran the profile runs described in paragraphs 306-309. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.) These profiles runs are test reactions, as they were carried out to determine results of varying reaction conditions. (Sept. Tr. (Gokel) 425:22-24.)

Sandoz's Response:

Correctly construed, Sandoz's "large scale profile runs" are not "test reactions." Regardless, whether Sandoz's large scale profile runs meet the Court's construction of "test reaction" is irrelevant to the infringement inquiry, as Sandoz no longer employs the large scale profile runs described in its original ANDA [redacted] to manufacture its glatiramer acetate product. (Sept Tr. 1099:13-20 (Bishop).) Sandoz's former use of the large scale profile runs is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

Moreover, Teva's implication that Sandoz was attempting to mimic the process and parameters of Teva's patent by manufacturing copolymer-1 at certain molecular weights is misleading. In its ANDA, Sandoz made clear that it was attempting to "meet the *label claim* of 5000 – 9000 daltons." (PTX 214 at SDZ00000186 (emphasis added).) At all times, Sandoz has

sought to manufacture a generic Copaxone product equivalent to the label specification, and not to copy the process and product defined by Teva's patents.

407. The reaction conditions (*i.e.*, the time and temperature) from these test reactions were, in turn, applied to Sandoz's production batches. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.) Thus, the time and temperature of the HBr/acetic acid reaction that is used to manufacture Sandoz's production batches were determined beforehand.

Sandoz's Response:

Correctly construed, Sandoz's "large scale profile runs" are not "test reactions." Regardless, whether Sandoz's large scale profile runs meet the Court's construction of "test reaction" is irrelevant to the infringement inquiry, as Sandoz no longer employs the profile runs described in its original ANDA to manufacture its glatiramer acetate product. (Sept Tr. 1099:13-20 (Bishop).) Sandoz's former use of the large scale profile runs is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra*.

408. Sandoz therefore created production batches of copolymer-1 using an HBr/acetic acid reaction that took place for a time and at a temperature that were "determined beforehand by a reaction carried out to determine results of varying reaction conditions." (Sept. Tr. (Gokel) 423:1-4, 425:16-21.) Its current ANDA process therefore meets the "predetermined by test reaction" limitation in claims 1-2 of the '898 patent, claims 1-2 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent.

Sandoz's Response:

Correctly construed, Sandoz's large-scale "profile runs" are not "test reactions." Therefore, the large-scale profile runs used to determine the parameters for the Step 2 reaction do not set a time and temperature "predetermined by test reaction" as required by claims 1-2 of the '898 patent, claims 1-2 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent. Regardless, whether Sandoz's large scale profile runs meet the Court's construction of "test reaction" is irrelevant to the infringement inquiry, as Sandoz no longer employs the large

scale profile runs described in its original [redacted] to manufacture its glatiramer acetate product. (Sept. Tr. 1099:13-20 (Bishop).)

409. In addition, because the current Sandoz ANDA sets forth a time of 43-47 hours and a temperature of 20 ± 2°C, the particular time ("about 10-50 hours") and temperature ("about 20-28°C") limitations of claim 2 of the '898 patent and claim 2 of the '430 patent are met. (Sept. Tr. (Grant) 363:14-364:7; PTX 353 at SDZ00017631-32.)

Sandoz's Response:

Sandoz does not dispute the content of its original ANDA, but it is irrelevant to the infringement inquiry, as Sandoz no longer employs the Step 2 depolymerization process as described in its original [redacted] to manufacture its glatiramer acetate product. Sandoz's former use of depolymerization conditions is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

(2) Sandoz's Current Process, As Reflected in the Briefing Book, Does Not Meet the Test Reaction Limitations.

410. To date, Sandoz has not filed an amended ANDA that makes any of the changes that were proposed in its Briefing Book. (PTX 913.) Thus, the current ANDA as filed with the FDA comprises the 2007 original ANDA [redacted] The Court, therefore, will only consider the current ANDA as filed with the FDA in determining infringement. *See Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002) ("Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry.").

Sandoz's Response:

Teva's assertion that only the original ANDA must be considered in the Court's infringement analysis is incorrect. As the Federal Circuit has recognized, an infringement inquiry under 35 U.S.C. § 271(e)(2)(A) requires a comparison of the claims of the asserted patents against the product that is likely to be sold following FDA approval. *See Abbott Labs.*, 300 F.3d at 1373. Although Teva tries to portray the changes to Sandoz's process as "possible"

or "potential" changes that may or not be made, the Briefing Book is a formal communication to the FDA, and counsel for Teva admitted that submission of the briefing book "signals an amendment to the ANDA.":

> THE COURT: Am I correct, however slight, this is an amendment to the description of the Anda product?
>
> MS. HOLLAND: It is the briefing book that was submitted to the FDA.
>
> THE COURT: Does it signal a amendment?
>
> MS. HOLLAND: Yes.

(Pretrial Conf. Tr. 15:20-25.)

Further, in making its infringement determination, the Court may consider not just the ANDA itself, but also "materials submitted by the ANDA applicant in support of the ANDA, and any other relevant evidence submitted by the applicant or patent holder." *Bayer*, 212 F.3d at 1248-49. Thus, all evidence presented regarding the process Sandoz will use in preparing the product that will eventually be marketed may be considered in the Court's infringement analysis.

411. This conclusion is confirmed by the fact that during additional discovery ordered on the Briefing Book process, and during the trial itself, Sandoz and Momenta have continued to assert that their manufacturing process will change. In fact, Dr. Bishop testified at trial, without any documentary support, that Sandoz now intends to change the manufacturing process yet again so that the backup time and temperature model (as explained above at paragraphs 322-325 above) will be removed and that Sandoz will rely only on a backup viscometer. (Sept. Tr. (Bishop) 1105:12-25.)

Sandoz's Response:

Dr. Bishop's testimony is credible, supported by the Briefing Book, which is a formal communication to the FDA, and was not rebutted by Teva. The Court gave Teva an opportunity to take Dr. Bishop's deposition regarding the new changes and Teva chose not to present any evidence to rebut Dr. Bishop's testimony at trial. As Dr. Bishop made clear, the use of a backup viscometer to provide measurements in the event of a failure is the only alternative method

Sandoz employs in its Step 2 reaction. The time-temperature backup described above in the batch records, and which was not described in the Briefing Book, is no longer used by Sandoz. (Sept. Tr. 1105:1-8, 1106:4-14 (Bishop).) Sandoz's proposed and discontinued used of the time-temperature backup is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

412. Sandoz's expert Dr. Laird similarly testified that because the Sandoz process uses two viscometers, one has to be considered a backup, negating the need for the backup time and temperature model. Dr. Laird admitted, however, that the current batch record, which contains Sandoz's current manufacturing process, indicates that the second viscometer yields different readings than the first viscometer, and that the calculations necessary to use the second viscometer to determine when to stop the HBr/acetic acid reaction (assuming that such calculations even exist) are not contained in the batch record. (Sept. Tr. (Laird) 1163:2-1164:21.) Further, the batch record does not even refer to the second viscometer as a backup viscometer. (PTX 928 at MMT01707038.)

Sandoz's Response:

Teva continues to assert that there is a lack of certainty regarding the process that will be used to manufacture Sandoz's proposed product. But, as discussed above in Sandoz's Response to ¶ 23, no such uncertainty exists. The Briefing Book is a formal communication to the FDA Process 1.1.0, [redacted] will be the only process used by Sandoz to manufacture its glatiramer acetate product moving forward. (Sept. Tr. 1105:1-8 (Bishop).)

Dr. Bishop's testimony is credible and was not rebutted by Teva. The Court gave Teva an opportunity to take Dr. Bishop's deposition regarding the new changes and Teva chose not to present any evidence to rebut Dr. Bishop's testimony at trial. Further, it is unremarkable that an accused infringer, during the course of developing a product, would develop a noninfringing method of making the product at issue.

Moreover, the fact that the batch record does not explicitly refer to the second viscometer as a "backup" is inconsequential. The alternative method contained in Sandoz's original process

was never described in the records as a "backup," but Teva has not disputed that this was its intended purpose. (Sept. Tr. 434:21, 24-25, 435:6-7, 1161:13-14 (Teva counsel referring to the time-temperature model as a "backup process" and "backup model").) The use of a backup viscometer to provide measurements in the event of a failure, is the only alternative method Sandoz employs in its Step 2 reaction. The time-temperature backup described above is no longer used by Sandoz. (Sept. Tr. 1105:1-8, 1106:4-14 (Bishop).) Sandoz's proposed and discontinued used of the time-temperature backup is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

413. In light of this uncertainty surrounding Sandoz's ever-changing manufacturing process and in light of Federal Circuit precedent, the Court will use the process as currently submitted to the FDA to assess infringement. As concluded above, there is no dispute that the current process in the Sandoz ANDA meets all the limitations.

Sandoz's Response:

See Sandoz's Response to ¶¶ 410-412.

414. Even if the Court were to assess infringement based on the process that Sandoz proposed in the Briefing Book, that process also has a step in which protected copolymer-1 is reacted with HBr/acetic acid for a time and at a temperature "determined beforehand by a reaction carried out to determine results of varying reaction conditions."

Sandoz's Response:

In its Finding of Fact #321, Teva admits that Sandoz's Process 1.1.0, submitted in its Briefing Book, uses viscosity to determine the endpoint of its Step 2 depolymerization reaction, *rather than time:*

> "Momenta documents indicate that as time increases, the viscosity decreases. (PTX 914 at MMT01630951-53.) Thus, the longer Intermediate-1 reacts with HBr/acetic acid, the lower its viscosity. This enables Sandoz to use viscosity, which changes as a function of time, rather than time itself to monitor the progress of the reaction and determine when to stop it in order to obtain a glatiramer acetate having an average molecular weight of [redacted] daltons. (Sept. Tr. (Gokel) 430:7-16, 434:9-17.)" (emphasis added).

In addition, in its Finding of Fact # 320, Teva states unequivocally that "[t]he Step 2 reaction is stopped when the targeted viscosity value is reached for the Step 2 reaction temperature. (Sept. Tr. (Gokel) 430:17-431:24; PTX 914 at MMT01630952-953; PTX 928 at MMT01707035.)" Teva makes no argument that the endpoint of the reaction also occurs at a predetermined time.

415. While the Briefing Book indicates that Sandoz has proposed an in-process control to monitor the progress of the HBr/acetic acid reaction, the batch records set forth the actual details of the process. (PTX 928 at MMT01707032-40.) These batch records must be submitted to the FDA as part of any future amendment to Sandoz's ANDA. (Sept. Tr. (Laird) 1157:11-14.)

Sandoz's Response:

As discussed above in Sandoz's Response to ¶ 325, Dr. Bishop testified that Momenta's future records will be revised to remove the back-up time-temperature model:

> Well, we are updating our records to -- we successfully used viscosity during our process validation campaign earlier this year, and so we have this back up in the event that viscometry failed during those process validation runs, since it didn't fail, and we have confidence now in our ability to use viscometry as an in process control, we no longer need this methodology as a back up, and we will be taking that out of our process henceforth.

(Sept Tr. 1108:19-1109:1.)

Momenta's batch records moving forward will describe the use of a primary viscometer, along with a backup viscometer to provide measurements in the event of a failure. (Sept Tr. 1105:22-1106:15.)

Momenta and Sandoz's proposed (and discontinued) use of this model to bring a generic glatiramer acetate product to market is a classic example of the kind of conduct protected under the safe harbor provision of 271(e). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.* It is therefore irrelevant to the infringement inquiry.

Teva improperly cites the testimony of British process chemist Dr. Trevor Laird, who did not provide opinions as an expert in regulatory compliance, the ANDA process or communications with the FDA.

416. The batch record sets forth two models for how to determine the time and temperature of the HBr/acetic acid reaction. These two models are considered part of the same manufacturing process. (Sept. Tr. (Laird) 1158:17-1159:11.) Under both models described in the Briefing Book and accompanying batch records, the time and temperature are predetermined by a test reaction.

Sandoz's Response:

The use of a primary viscometer, along with a backup viscometer to provide measurements in the event of a failure, is the only method Sandoz employs for its Step 2 reaction. The time-temperature backup described above is not mentioned [redacted] and is no longer used by Sandoz. (Sept. Tr. 1105:1-8 (Bishop).) Moreover, Sandoz's prior investigation on how to manufacture copolymer-1 is protected under the safe harbor provision of 35 U.S.C. § 271(e)(1) (2006). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

417. The "viscometer" model comprises a table of temperatures and viscosity values. (Sept. Tr. (Gokel) 430:7-434:22; PTX 914 at MMT01630951-52; PTX 928 at MMT01707035.) These data are based on test reactions, as that term has been construed by the Court. (Sept. Tr. (Gokel) 436:18-439:10; PTX 923 at MMT01694006, 106-124.) Dr. Laird agreed that these data were obtained from test reactions. (Sept. Tr. (Laird) 1160:4-8.) The "time and temperature" model comprises a table of times and temperatures. (Sept. Tr. (Gokel) 435:14-436:3; PTX 914 at MMT01630954-55; PTX 928 at MMT01707036.) These data are also based on test reactions. (Sept. Tr. (Gokel) 436:18-439:10; PTX 923 at MMT01694006, 106-124.)

Sandoz's Response:

Sandoz maintains that its proposed construction of the "predetermined by test reaction" limitation is the correct one. Although Dr. Laird stated that the sample tests are "test reactions" under the Court's construction, these sample tests, correctly construed, would not satisfy the "predetermined by test reaction" limitation. Further, Teva must show that Sandoz uses *both* a

time and temperature predetermined by test reaction in order to meet its burden on this claim limitation. Teva relies on previous testing of different batches of copolymer-1 as a "test reaction" for the in-process viscosity control, but that testing does not predetermine the time *and* temperature to react protected copolymer-1 with HBr/acetic acid. If it did, there would be no need for the viscosity in-process control. Moreover, the testing of prior batches for purposes of regulatory approval is immune under 35 U.S.C. § 271(e)(1) (2006). *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.* And, as discussed above in Sandoz's Response to ¶ 416, Sandoz will no longer use the "time and temperature" model described above as a backup to its in-process viscometry control.

418. The temperature in both models is predetermined, as there is a pre-set temperature target of 21°C, and each model contains a column that identifies particular temperatures in tenths of a degree. (Sept. Tr. (Gokel) 432:11-23, 435:14-436:3; PTX 914 at MMT01630954-55; PTX 928 at MMT01707035-36.)

Sandoz's Response:

Undisputed. However, Teva must show that Sandoz uses *both* a time and temperature predetermined by test reaction in order to meet its burden on this claim limitation.

419. Time is predetermined according to the viscometer model because there is a predetermined relationship between time and viscosity, so that no matter which model is used, the time has been determined beforehand. (Sept. Tr. (Gokel) 436:4-17.) Even if time is not literally predetermined in the viscometer model, the overall process of determining when to stop the HBr/acetic acid reaction in order to obtain a copolymer-1 having an average molecular weight of 7300 daltons is insubstantially different. *See Adams Respiratory Therapeutics*, 616 F.3d at 1293 ("The proper inquiry is whether the accused value is insubstantially different from the claimed value."); *Boehringer Ingelheim Vetmedica*, 320 F.3d at 1351 ("Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are 'insubstantial' to one of ordinary skill in the art.").

Sandoz's Response:

Teva itself admits that Sandoz's Step 2 process uses viscosity, which measures a physical property of the solution to determine the endpoint, rather than time itself. (Teva FFCOL No. 321.) And, as discussed *infra* in Sandoz's Response to ¶ 421, Teva presented no evidence to

support its theory that the two processes perform substantially the same function in substantially the same way to achieve substantially the same result. *See Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, (1950). Nor could it, as Teva's expert has admitted that the two methods of determining the endpoint of the reaction are "fundamentally different":

> Q. Is there any difference in the accuracy?
>
> A. Well, I think the -- I think the key difference in the accuracy will be dependent, in the case of a clock, on what kind of a clock, what kind of a movement, all that -- all that sort of stuff.
>
> And in a viscometer it's a -- it's a fundamentally different kind of apparatus which will have -- which will have different variables associated with it as a -- as a specification.

Declaration of Karen Hagberg in Support of Sandoz's Opp. ("Hagberg Decl.") Ex. 1 (Deposition Transcript of George Gokel, Ph.D., dated Sept. 4, 2011 ("Gokel Dep."), at 302:22-303:17.)

420. The time and temperature model, however, could be used for any batch, and therefore must be considered for infringement. There is no argument that the times in the time and temperature model have not been predetermined. (Sept. Tr. (Gokel) 436:9-12.)

Sandoz's Response:

As discussed above, the time and temperature model is no longer employed by Momenta in its Step 2 depolymerization process. Teva's assertion that it "could be used for any batch" is therefore incorrect. Sandoz's proposed and discontinued used of the time and temperature model is protected under the safe harbor provision of 271(e), and is therefore irrelevant to the infringement inquiry. *See* Sandoz's Response to Section VI.B.ii.2.a, *supra.*

421. Even if the time and temperature model were not considered in determining whether the viscometer model literally meets the "predetermined by test reaction" limitation of the claimed methods, determining when to stop the reaction in order to obtain a copolymer-1 having an average molecular weight of 7,300 daltons by using test reactions to predetermine a relationship between the temperature and viscosity and the time to stop the reaction is insubstantially different from using test reactions to predetermine a pre-set time to stop the reaction. In either case, a copolymer-1 having an average molecular weight of 7,300 daltons is obtained.

<u>*Sandoz's Response:*</u>

The question of whether a product or process infringes under the doctrine of equivalents is a fact-intensive inquiry. *See Graver Tank & Mfg. Co.*, 609. But Teva provides no evidence of equivalence, and simply asserts that Sandoz's viscometry method is "insubstantially different" from the Court's construction of a process at a temperature and for a time predetermined by test reaction.

Teva's assertion that the two processes are substantially similar is directly contradicted by the deposition testimony of its expert, Dr. Gokel, who testified that a viscometer is "fundamentally different" from a clock:

> Q: Will there be any differences, in your opinion, between using those different methods?
>
> A: I don't know what you mean by "any differences."
>
> Q: Is there any difference in the accuracy?
>
> A: Well, I think the -- I think the key difference in the accuracy will be dependent, in the case of a clock, on what kind of a clock, what kind of a movement, all that -- all that sort of stuff. *And in a viscometer it's a -- it's a fundamentally different kind of apparatus which will have -- which will have different variables associated with it as a -- as a specification. So there could be -- there could certainly be some differences.*

(Gokel Dep. at 302:22-303:17 (emphasis added).)

Further, Teva's assertion that equivalence should be found solely because "in either case, a copolymer-1 having an average molecular weight of 7,300 daltons is obtained" falls short. In order to prove infringement under the doctrine of equivalents, Teva must show that the accused product performs substantially the same function in substantially the same way to achieve substantially the same result. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1351 (Fed. Cir. 2003) (applying function-way-result test to find no equivalence); *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 813 (Fed. Cir. 2002). Even if

the resulting product may be similar, Teva must also prove that Sandoz's process performs substantially the same *function* in substantially the same *way*. Teva has presented only conclusory attorney argument, and no actual evidence, on any of these three elements.

Moreover, the two processes are not equivalent because the viscometry method offers significant advantages over the time-temperature model claimed in the patents in suit, including less waste and greater accuracy. (Sept. Tr. 1099:5-12 (Bishop); 1135:18-1136:2, 1136:12-1137:5 (Laird).) Dr. Gokel recognized that the viscosity method, which allows continuous in-process monitoring of the depolymerization reaction, has advantages over a test reaction run beforehand. (Gokel Dep., Sept. 4, 2011, at 71:18-72:13 (a "fundamental advantage" is that the operator "would be able to get closer to the endpoint.")

Further, as the Federal Circuit has explained:

> [a]pplication of the doctrine of equivalents is the exception, ... not the rule, for if the public comes to believe (or fear) that the language of patent claims can never be relied on, and that the doctrine of equivalents is simply the second prong of every infringement charge, regularly available to extend protection beyond the scope of the claims, then claims will cease to serve their intended purpose. Competitors will never know whether their actions infringe a granted patent.

Wallace London Clemco Prods. v. Ccarswon Pirie Scott Co., 946 F.2d 1534, 1538 (Fed. Cir. 1991).

In the absence of any actual evidence of equivalence, the Court should reject Teva's attempt to extend its patent protection beyond the actual scope of the claims.

422. Thus, the process that Sandoz has proposed in its Briefing Book meets the "predetermined by test reaction" limitation in claims 1-2 of the '898 patent, claims 1-2 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent, either literally or under the doctrine of equivalents.

Sandoz's Response:

As discussed above, Teva has not met its burden to prove by a preponderance of the evidence that Sandoz' proposed product meets the time and temperature predetermined by test

reaction limitations in claims 1-2 of the '898 patent, claims 1-2 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent.

423. In addition, because the Briefing Book process under either model targets a temperature of [redacted] and can range only from [redacted] C, the temperature limitation ("about 20-28°C") of claim 2 of the '898 patent and claim 2 of the '430 patent is met. Further, because the time and temperature model sets forth a range of times between [redacted] hours, the time limitation of "about 10-50 hours" of claim 2 of the '898 patent and claim 2 of the '430 patent is met.

Sandoz's Response:

Sandoz does not dispute the contents of the Briefing Book. However, Teva must show that Sandoz's uses *both* a time and temperature predetermined by test reaction in order to meet its burden on this claim limitation.

(iv) Sandoz's Treatment Limitations

424. Based on Dr. Lisak's testimony, Sandoz's proposed product meets the "method of treating multiple sclerosis" limitation found in claim 1 of the '476 patent; the "administering to a subject in need thereof" limitation found in claim 1 of the '476 patent; the "pharmaceutically effective amount" limitation found in claim 1 of the '476 patent and claim 1 of the '161 patent; the "treatment of multiple sclerosis" limitation found in claim 1 of the '161 patent; the "suitable for treating multiple sclerosis" limitation found in claim 1 of the '539 patent; the "dose therapeutically effective to treat multiple sclerosis" found in claim 12 of the '539 patent; the "a method for treating a patient suffering from multiple sclerosis" found in claims 23, 30, and 31 of the '539 patent; the "administering to a patient in need thereof" limitation found in claims 23, 30, and 31 of the '539 patent; and the "suitable for treating multiple sclerosis" limitation found in claim 1 of the '098 patent. (Sept. Tr. (Lisak) 137:5-147:19; PTX 985 at 20.)

Sandoz's Response:

Because there is no direct infringement, there can be no inducement of infringement.

425. In addition, based on the stipulation entered into by Sandoz, Sandoz's proposed product meets the limitations of "pharmaceutical composition" and "pharmaceutically acceptable excipient" in claims 12, 23, 30, and 31 of the '539 patent. (PTX 936.)

Sandoz's Response:

Because there is no direct infringement, there can be no inducement of infringement.

426. Finally, Sandoz will induce physicians to infringe the '476 and '539 patents should its ANDA be approved. Sandoz knew of those patents before filing its ANDA, as it filed

a certification with the FDA and sent a notice letter to Teva specifically referencing the patents-in-suit, including the '476 and '539 patents. (*See* PTX 254 at SDZ00016843; Pretrial Order at ¶¶ 89-90, 94-95.) Sandoz's proposed product label will induce doctors to prescribe its ANDA product for treatment of multiple sclerosis and thereby induce infringement of claim 1 of the '476 patent and claims 23, 30, and 31 of the '539 patent. *See AstraZeneca LP*, 633 F.3d at 1060-61 ("The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [the alleged infringer's] affirmative intent to induce infringement."); *see also Wyeth*, 703 F. Supp. 2d at 521 ("Sandoz's seeking ANDA approval and proposing draft labeling that will instruct how to engage in infringing uses constitute the affirmative steps required to show inducement.").

Sandoz's Response:

There is no direct infringement because Sandoz does not intend to sell "copolymer-1" as that term is defined in the patents-in-suit, or sell copolymer-1 with the required weight average molecular weight of less than 10 kDa. *See* Sandoz's Response to ¶¶ 282-287, 391-401, *supra*. Absent a finding of direct infringement, Sandoz cannot induce infringement.

(v) Sandoz Does Not Infringe Any of the Asserted Claims.

427. In sum, based on the testimony of Dr. Lisak, Dr. Grant, Dr. Sampson, and Dr. Gokel, the documentary evidence they referred to during their testimony, and Sandoz's stipulations, Sandoz's manufacture and sale of its proposed glatiramer acetate product would infringe each of the asserted claims.

Sandoz's Response:

Teva's claims under 35 U.S.C. § 271(a) fail as a matter of law because it has not shown that Sandoz's proposed product meets each and every limitation of the asserted claims.

Specifically, Teva did not prove by a preponderance of the evidence that the product likely to be sold by Sandoz, when approved by the FDA, will meet the claim limitation requiring the use of a test reaction to predetermine both time and temperature, as required by claims 1-2 of the '898 Patent, claims 1-2 of the '430 Patent, claim 1 of the '476 Patent, and claim 1 of the '161 Patent.

Teva also did not prove by a preponderance of the evidence that the product likely to be sold by Sandoz, when approved, met the "molecular weight" claim limitations because Teva

failed to show that Sandoz's proposed product will have a weight average molecular weight of less than 10 kDa, as required by all of the asserted claims.

Teva did not prove by a preponderance of the evidence that Sandoz's proposed product met the definition of "copolymer-1" because Teva failed to show that the product is "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine a molar ratio of approximately 6:2:5:1, respectively," as required by all asserted claims.

VII. FINDINGS OF FACT AND CONCLUSIONS OF LAW RELATING TO DEFENDANTS' INDEFINITENESS AND ENABLEMENT DEFENSES

428. Over the course of this litigation Defendants have made two primary indefiniteness arguments. First, Defendants argued that a person of ordinary skill in the art would not be able to understand the meaning of the molecular weight claim terms. Second, Defendants have argued that a person of ordinary skill in the art would not be able to determine whether a copolymer-1 sample met the claim limitations because the "standards and conditions" for molecular weight analysis were not identified in the patent specification.

<u>*Sandoz's Response:*</u>

Teva conflates the indefiniteness arguments that Sandoz has made and continues to make in this case. The asserted claims are indefinite, because the claims do not identify the SEC calibration standards against which the claimed molecular weights are to be measured. The evidence at trial established that different, "appropriate," calibration standards can lead to very different molecular weight results for copolymer-1. (*See, e.g.*, Sept. Tr. 1293:3-7 (Scandella); 1824:3-25 (Wall); Sandoz's Opening FFCOL ¶¶ 77-78, 85-114, 123-132.) Therefore, by claiming copolymer-1 with specific molecular weights and molecular weight distributions and not specifying the calibration standards by which to obtain those molecular weights, the claims are insolubly ambiguous.

429. The Court's Claim Construction Order largely disposed of both of these arguments. First, the Court held that the claim terms related to "average molecular weight" were amenable to construction, and construed "average molecular weight" to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (No. 08-cv-7611, D.I. 273, No. 09-cv-8824, D.I. 194, Claim Construction Order at 40 & n.10); *Exxon*

Research & Eng'g Co. v. United States, 265 F.3d 1371, 1375 (Fed. Cir. 2001) (finding that claims are indefinite only if reasonable efforts at claim construction prove futile). Second, the Court analyzed and rejected Defendants' "standards and conditions" indefiniteness argument. (Claim Construction Order at 31-36.)

Sandoz's Response:

Sandoz does not dispute that the Court construed "average molecular weight" to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column," but that construction remains indefinite. In August 2011, the Federal Circuit held that "a construed claim can be indefinite if the construction remains insolubly ambiguous, meaning it fails to provide sufficient clarity about the bounds of the claim to one skilled in the art." *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, No. 2010-1183, 2011 U.S. App. LEXIS 17826, at *19 (Fed. Cir. Aug. 26, 2011). Because there were multiple appropriate ways to calibrate an SEC column in 1994, and the resulting molecular weights would not have been the same, the term "appropriately calibrated suitable gel filtration column" in the Court's claim construction remains insolubly ambiguous. (Sept. Tr. 1293:3-7 (Scandella); 1824:3-25 (Wall).) The Court's analysis of the "standards and conditions" issue in the August 24, 2011 Claim Construction Order pre-dates both the *Star Scientific* case and the evidence presented at trial on this issue. Documents and testimony from the trial provide clear and convincing evidence that "average molecular weight," as construed, "fails to provide sufficient clarity about the bounds of the claim to one skilled in the art." *Star Scientific*, 2011 U.S. App. LEXIS 17826, at *19. *See* Sandoz's Opening FFCOL ¶¶ 54-148, 164-167.

430. At trial, Mylan did not pursue any indefiniteness theory. Sandoz did not pursue the argument that the failure to disclose specific "conditions" for the operation of the SEC column rendered the claims indefinite or not enabled. Rather, Sandoz pursued only the argument that the claims are invalid because the patent specification does not identify the molecular weight calibration "standards" or how to measure the molecular weights of such standards.

<u>*Sandoz's Response:*</u>

At trial, Sandoz emphasized the failure of the patents to disclose SEC calibration standards. (*See, e.g.*, Sept. Tr. 1227:21-1228:11 (Scandella); 1764:18-1765:25 (Wall).) Sandoz, however, maintained its position at trial regarding the importance of stating the SEC conditions for copolymer-1 analysis. For example, Dr. Scandella testified that the patent specification "doesn't disclose how to calibrate that Superose 12 column, or what specific conditions were used for the analysis." (Sept. Tr. 1227:14-15.) He also testified that if copolymer-1 self-standards were the intended calibration method of the asserted patents, information about the SEC conditions should have been included in the patents:

> Q. What information would you expect to see in the patents if the patentees intended the claimed molecular weights to be reproduced using self standards?
>
> A. At a minimum, I would expect to see the conditions of the chromatography, because especially for a sample like cop-1, the conditions can affect the structure of the molecules and how they're going to behave on the column, and I would also expect to see information about how the column was standardized or calibrated.

(Sept. Tr. 1252:10-18.) He further testified that conditions are important in deciphering the possible structures of copolymer-1 in solution: "I think one needs to specify the conditions in order to know, to know what we're talking about." (Sept. Tr. 1322:2-3.) In addition, Dr. Wall testified: "If, on the other hand, you disclose or tell other investigators what your standards are and what your conditions are for running the column with the information about the column being a Superose 12 column, they would be able to reproduce your experiment and get the same or a very similar result." (Sept. Tr. 1766:22-1767:2.)

431. Sandoz has not argued that any asserted claims of the '898 patent are invalid as indefinite or not enabled. (Sept. Tr. (Scandella) 1224:13-21; Sept. Tr. (Wall) 1764:6-17.)

Sandoz's Response:

Undisputed.

432. The bar for demonstrating that claims are invalid due to indefiniteness or lack of enablement is, however, set high. *Microsoft Corp. v. i4i Limited Partnership*, 131 S. Ct. 2238, 2246-47 (2011); *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1338-39 (Fed. Cir. 2008). The clear and convincing standard is a heightened standard of proof, and a defendant raising an invalidity defense bears a "heavy burden of persuasion." *Microsoft Corp.*, 131 S. Ct. at 2246-47.

Sandoz's Response:

Undisputed that the standard is clear and convincing evidence. Sandoz has met this burden with ample clear and convincing evidence regarding the inability of one of ordinary skill in the art to understand the scope of the molecular weight claims or reproduce the claimed invention without knowing the calibration standards and other aspects of the calibration procedure used by the patentees. (*See* Sandoz's Opening FFCOL ¶¶ 54-148, 164-167.)

433. "When, as here, a party asserts invalidity of a patent and bases that assertion on evidence, including prior art references, that was before the patent examiner when he allowed the patent claims, the difficulty of overcoming the presumption of validity is greater than it would be if the evidence relied on was not before the examiner." *In re Omeprazole Patent Litigation*, 490 F. Supp. 2d 381, 500 (S.D.N.Y. 2007) (citing *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1358-60 (Fed. Cir. 1984)); *see also Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011).

Sandoz's Response:

The standard is clear and convincing evidence regardless of whether the art was before the PTO. Moreover, the documentary and testimonial evidence of indefiniteness and lack of enablement in this case was not before the patent examiner when he allowed the claims. The Supreme Court has held that "new evidence supporting an invalidity defense may 'carry more weight' in an infringement action than evidence previously considered by the PTO." *Microsoft*, 131 S. Ct. at 2251. *See also Tokai Corp*, 632 F.3d at 1367 ("An added burden of deference to

the PTO is not required, however, with respect to invalidity arguments based on evidence that the PTO did not consider.”).

434. Defendants have failed to carry their burden of proving indefiniteness or non-enablement by clear and convincing evidence. As set forth below, the evidence offered at trial further confirms what this Court has previously stated: “Sandoz and Mylan argue that every use of the term ‘molecular weight’ in the patent claims is indefinite. The Court disagrees.” (Claim Construction Order at 16.)

Sandoz’s Response:

Sandoz has met its burden with clear and convincing documentary and testimonial evidence regarding the inability of one of ordinary skill in the art to understand the scope of the molecular weight claims or reproduce the claimed invention without knowing the calibration standards and other aspects of the calibration procedure used by the patentees. (*See* Sandoz’s Opening FFCOL ¶¶ 54-148, 164-167.) As explained in detail below, the evidence proffered by Teva is insufficient to refute Sandoz’s evidence.

A. Legal Principles—Indefiniteness

435. The determination of whether a claim term is amenable to construction, and therefore definite, is a matter of law. *See, e.g.*, *Kinetic Concepts, Inc. v. Blue Sky Med. Group*, 554 F.3d 1010, 1022 (Fed. Cir. 2009). To establish indefiniteness, Defendants must prove by clear and convincing evidence that the terms “average molecular weight” and “copolymer-1 having a molecular weight” cannot be construed in the context of the patents-in-suit. The critical question for indefiniteness is whether a person of skill in the art would understand the meaning of the claims. *Id.*

Sandoz’s Response:

To establish indefiniteness, Sandoz need not prove that the terms “average molecular weight” and “copolymer-1 having a molecular weight” cannot be construed. Rather, as the Federal Circuit has explained, “a construed claim can be indefinite if the construction remains insolubly ambiguous, meaning it fails to provide sufficient clarity about the bounds of the claim to one skilled in the art.” *Star Scientific*, 2011 U.S. App. LEXIS 17826 at *19. Thus, Sandoz need only prove that the construction of these claim terms remains insolubly ambiguous. *Id.*

Sandoz has done so, with ample documentary and testimonial evidence regarding the inability of one of ordinary skill in the art to understand the scope of the molecular weight claims. (*See* Sandoz's Opening FFCOL ¶¶ 77-78, 85-114, 123-132, 164-167, 170.). Because there were multiple ways to appropriately calibrate an SEC column in 1994, and the resulting molecular weights would not have been the same, the term "appropriately calibrated suitable gel filtration column" is insolubly ambiguous. (Sept. Tr. 1293:3-7 (Scandella); 1824:3-25 (Wall).)

436. A claim is not indefinite merely because the meaning of the claim is not plain on its face. *Exxon Research & Eng'g Co.*, 265 F.3d at 1375. "If the meaning of the claim is discernable, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, [the Federal Circuit has] held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Id.* Thus, only claims that are "insolubly ambiguous" even after the Court uses all tools at its disposal to try to construe the claims are invalid as indefinite. *See Source Search Techs., LLC v. LendingTree LLC*, 588 F.3d 1063, 1076 (Fed. Cir. 2009); *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1371 (Fed. Cir. 2008); *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 780 (Fed. Cir. 2002).

Sandoz's Response:

In August 2011, the Federal Circuit held that "a construed claim can be indefinite if the construction remains insolubly ambiguous, meaning it fails to provide sufficient clarity about the bounds of the claim to one skilled in the art." *Star Scientific*, 2011 U.S. App. LEXIS 17826 at *19. Thus, even if the claim can be construed, it may be still be held indefinite if the construction remains insolubly ambiguous. *Id.* The Federal Circuit has therefore made clear that the "not amenable to construction" test is not the only test for indefiniteness. *See also Source Search*, 588 F.3d at 1076 ("Only claims 'not amenable to construction' or 'insolubly ambiguous' are indefinite.").

437. To satisfy Section 112's "definiteness requirement, the boundaries of the claim, as construed by the court, must be discernible to a skilled artisan based on the language of the claim, the specification, and the prosecution history, as well as her knowledge of the relevant field of art." *Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1350 (Fed. Cir. 2010); (Claim Construction Order at 5.) In addition, "the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite." *Exxon*

Research & Eng'g Co., 265 F.3d at 1379; Claim Construction Order at 5.

Sandoz's Response:

Undisputed.

B. Legal Principles—Lack of Enablement

438. A patent claim is invalid for lack of enablement only if the claimed invention cannot be practiced without "undue experimentation" by a person of ordinary skill in the art. *Monsanto Co. v. Scruggs*, 459 F.3d 1328, 1337-38 (Fed. Cir. 2006); *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). What constitutes undue experimentation, as explained by the courts, "requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 858 F.2d at 737.

Sandoz's Response:

Undisputed.

439. The Federal Circuit has made clear that a patent specification is not a product specification. *Koito Mfg. Co. Ltd. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1156 (Fed. Cir. 2004). Although a patent specification must provide an enabling disclosure, a claim does not fail the enablement requirement simply because details that would be known and available to those of skill in the art are not set forth in the patent specification. *Singh v. Brake*, 317 F.3d 1334, 1345 (Fed. Cir. 2002); *Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 1345 (Fed. Cir. 2000); *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) (holding that the patent was enabled because the methods were known in the art, and stating that "a patent need not teach, and preferably omits, what is well known in the art.").

Sandoz's Response:

The SEC calibration standards and the method by which to determine the molecular weights of the standards are not production details; they are essential pieces of information needed to reproduce the claimed invention. (Sept. Tr. 1227:21-1228:11; 1253:4-12; 1273:13-23 (Scandella); 1764:18-1765:25; 1826:4-14 (Wall).) Furthermore, the Federal Circuit has held that omission of some production details can be non-enabling. In *Koito*, the court held that "*[u]nless there is evidence to the contrary*…the lack of certain production details does not indicate failure of enablement" and concluded that "Koito simply did not provide evidence at trial that the

production details omitted would have made one of ordinary skill in the art unable to practice the claimed invention without undue experimentation." 381 F.3d at 1156 (emphasis added). Here, Sandoz provided clear and convincing evidence that the omission from the patents of the SEC calibration standards precludes one of ordinary skill in the art from reproducing the claimed invention. (Sandoz's Opening FFCOL ¶¶ 54-132, 156-161.)

A patentee "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010). As the Federal Circuit has explained, "omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). *See also id.* ("[A] specification need not disclose what is well known in the art. However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure.") (internal citation omitted).

440. Determining whether required experimentation is "undue" requires consideration of the technology at issue and the level of skill in the art. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (finding claims to a vaccine were enabled where the skill level in the art was high, and agreeing with the BPAI that "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered 'undue' in this art."); *Monsanto Co.*, 459 F.3d at 1338 (specific DNA sequence was not required for enablement in part because of the level of skill in the art); *In re Wands*, 858 F.2d at 740 (weighing the high level of skill in the art in holding that undue experimentation would not be required).

Sandoz's Response:

Determining whether required experimentation is undue involves consideration of the *Wands* factors, which address more than just "the technology at issue and the level of skill in the art." *In re Wands*, 858 F.2d at 737.

441. As a matter of law, a person of ordinary skill in the art is deemed familiar with *all* pertinent prior art. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *In re Omeprazole Patent Litig.*, 490 F. Supp. 2d at 511.

Sandoz's Response:

Undisputed.

442. Furthermore, the Federal Circuit has held that evidence regarding work done in a patentee's laboratory is insufficient as a matter of law to show lack of enablement where there is no evidence that the persons performing the work were persons of ordinary skill in the art. *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998) ("Because it is imperative when attempting to prove lack of enablement to show that *one of ordinary skill in the art* would be unable to make the claimed invention without undue experimentation, . . . CellPro's evidence concerning [the inventor's] subsequent work is insufficient as a matter of law.").

Sandoz's Response:

The *Johns Hopkins* court did not hold that all persons working in a patentee's laboratory must have been persons of ordinary skill in the art for the laboratory work to be relevant to the undue experimentation inquiry. Moreover, the court did not hold that the data obtained by scientists in patentee's laboratory should be disregarded. Nor did the court hold that expert testimony concerning what one of ordinary skill in the art would have done at a certain point in time could not be informed by what those in the patentee's laboratory actually did. The Federal Circuit has explicitly held that "an inventor's failed attempts to practice an invention are relevant evidence of non-enablement." *Novo Nordisk Pharm., Inc. v. Bio-Technology Gen. Corp.*, 424 F.3d 1347, 1362 (Fed. Cir. 2005); *see also AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244-45 (Fed. Cir. 2003); *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372-73 (Fed. Cir. 1999).

443. In determining whether a claim is enabled, courts have looked to the following

factors, known as the "*Wands*" factors:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d at 737.

Sandoz's Response:

Undisputed.

C. Findings of Fact on Definiteness and Enablement

(i) Person of Ordinary Skill

444. The testimony by the experts at trial was unanimous on at least one issue: that the level of skill in the art of the patents-in-suit was (and is) high. Particularly relevant to this analysis, all experts agree that a person of ordinary skill would have specific experience and skills in size exclusion chromatography. (*See* Sept. Tr. (Grant) 189:22-190:6; PTX 986 at 3 (having an "advanced degree or equivalent in a chemical or biological discipline, and significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides"); Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9 ("a Ph.D. in chemistry, biochemistry or related field with a minimum of three years of experience in chromatography and specifically in size exclusion chromatography of macromolecules."); Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4 (definition includes "extensive experience in the synthesis, fractionation, and characterization of polymers, such as their hydrodynamic and structural properties, as applied to proteins, synthetic peptides and/or polydisperse peptide mixtures, as well as experience in the determination of the molecular weight distribution and average molecular weights of such polymers by methods such as size exclusion chromatography (SEC), and an understanding of how the standards and conditions used in the molecular weight determination affect the results obtained.").

Sandoz's Response:

Sandoz's experts did not testify that the level of skill was "high." Nor did any of the experts testify that one of ordinary skill in the art "would have specific experience and skills in size exclusion chromatography." Dr. Scandella's and Dr. Wall's definition of a person of ordinary skill in the art includes a person who has supervised or directed a research laboratory that conducts chromatography. (Sept. Tr. 1190:15-20 (Scandella), 1756:2-15 (Wall).) Dr.

Zeiger's definition includes "experience in the determination of…average molecular weights…by methods *such as* size exclusion chromatography…." (Sept. Tr. 809:10-811:15; DTX 4030 at 4 (emphasis added).) And Dr. Grant did not mention SEC at all in his definition. (Sept. Tr. (Grant) 189:22-190:6; PTX 986 at 3.)

(ii) A Person of Skill in 1994 Could Not Determine Whether Copolymer-1 Was Made According to the Claims

445. In 1994, a person of skill in the art could have determined the molecular weight of a copolymer-1 sample using SEC based on the teachings in the patents-in-suit without undue experimentation. (Sept. Tr. (Grant) 1422:9-14.) Indeed, Mylan's expert witness, Dr. Hurwitz, admitted that in 1994, a person of ordinary skill in the art could have used SEC on a sample of copolymer-1 to determine its peak molecular weight:

> Q. The person of ordinary skill in 1994 could perform a measurement using SEC on a sample of copolymer-1 to determine the peak molecular weight, correct?
> A. Yes.

(PTX 959 (Hurwitz Dep.) at 131:12-16.)

Sandoz's Response:

Sandoz does not dispute that a person of ordinary skill in the art could have used SEC on a sample of copolymer-1 in 1994 and obtained a peak molecular weight determination according to the selected calibration standard. That determination, however, would not be the same as that for a copolymer-1 sample made according to the claims, because the patents do not disclose the calibration standards selected by the patentees. The evidence adduced at trial demonstrates that SEC analysis of a given copolymer-1 sample can yield a range of molecular weight values depending on the selected calibration standards. (Sandoz's Opening FFCOL ¶¶ 77-78, 85-114, 123-132.) Because the patents lack any information on the calibration standards, one of skill in the art cannot determine whether a copolymer-1 sample has been made according to the claims. (Sept. Tr. 1825:5-19 (Wall); Sandoz's Opening FFCOL ¶¶ 156-158.)

446. In order to accurately measure the molecular weight of copolymer-1, a person of

skill in the art could have used either self-standards or universal calibration. (Sept. Tr. (Grant) 1399:18-1400:13; PTX 990 at 2.) Both techniques were well-known to persons of skill in the art in 1994.

Sandoz's Response:

The term "accurately" is not defined in this paragraph nor in the cited testimony and is not part of the Court's claim construction for the "molecular weight" limitations. To the extent Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is wrong. As Sandoz's experts testified, "SEC doesn't yield absolute molecular weights. It's not an absolute measurement method. So one wouldn't assume that the value that came from a size exclusion column was an absolute value." (Sept. Tr. 1292:21-1293:1 (Scandella); 1825:1-4 (Wall).) Sandoz's experts also explained that neither the use of self-standards nor universal calibration would have enabled the claims. (Sandoz's Opening FFCOL ¶¶ 122-142.) Moreover, universal calibration was not a common and widespread technique in the field of biotechnology and pharmaceutical products in 1994 or 1995. (Sept. Tr. 1284:13-18 (Scandella).) And it was not used by Teva's own expert Dr. Grant in 1994 or 1995. (Sept. Tr. 268:25-269:8 (Grant).)

(1) Self-Calibration

447. For conventional SEC, it was known in 1994 that in order to accurately correlate the retention time of the molecules coming out of an SEC column with their molecular weights, the column must be calibrated using standards with the same hydrodynamic characteristics as the sample being measured. (Sept. Tr. (Grant) 1412:6-1413:16; Sept. Tr. (Scandella) 1314:15-1316:24; PTX 961 (Kota Dep.) 18:3-14; PTX 962 (B. Rao Dep.) at 75:6-76:10, 78:14-80:5; PTX 973 (Venkataraman Dep.) at 108:20-109:23; PTX 974 (Wallingford Dep.) 146:9-149:7; PTX 317 at MYL0000111; PTX 553 at 72.)

Sandoz's Response:

To the extent Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is wrong, as explained above. In addition, in using SEC to obtain molecular weight data, it is not necessary for the standards to have the same hydrodynamic

volume as the sample being analyzed. (Sept. Tr. 1292:13-15 (Scandella).) As Dr. Scandella testified:

> Often one doesn't know what the hydrodynamic volume of a sample is, and in the biotechnology industry size exclusion chromatography is used normally using protein standards, and one reports the results as relative to the protein standards, understanding that the shape of the molecule that you're studying may not be exactly the same as the protein standards.

(Sept. Tr. 1292:15-20 (Scandella).)

448. A person of ordinary skill in the art in 1994 would have understood that the polypeptides in copolymer-1 are not globular. (Sept. Tr. (Grant) 1425:12-23; PTX 970 (Svec Dep.) at 395:21-395:24, 396:16-397:8, 397:11-397:17, 397:24-398:15.) For this reason, a person of skill in the art would have understood that globular protein standards do not have the same hydrodynamic characteristics as copolymer-1 and would therefore be inappropriate for use in conventional calibration for copolymer-1, as they would not provide an accurate molecular weight. (Sept. Tr. (Grant) 272:19-273:25, 1399:8-17; PTX 970 (Svec Dep.) at 394:23-395:3, 398:16-398:25.)

Sandoz's Response:

In 1994, a person of ordinary skill in the art would not have known the shapes that copolymer-1 would assume in solution. (Sept. Tr. 1205:4-8 (Scandella).) In an SEC column, it is "difficult to predict what structure [a] polypeptide is going to have at any time." (Sept. Tr. 1200:12-13 (Scandella).) It is "almost certain" that the copolymer-1 molecules in an SEC column will adopt more than a single shape. (Sept. Tr. 1200:14-18 (Scandella).)

In addition, the Teva scientists and the scientists at Teva's consultant, W.R. Grace, both calibrated the SEC column with commercially available globular protein standards when first attempting to determine the molecular weight of copolymer-1. (DTX 3275 at TEV000304991-92; Sept. Tr. 1230:13-1231:6 (Scandella); 1498:1-18 (Grant); DTX 1762 at TEV000360359; Sept. Tr. 1239:3-24 (Scandella); 284:7-11; 1501:22-25 (Grant).)

To the extent Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is wrong, as explained above.

Calibrating the SEC column with commercially available protein standards would have been a reasonable choice for a person of ordinary skill in the art attempting to measure the molecular weight of copolymer-1 in this timeframe, because proteins "are polypeptides and…there were no other polypeptide molecular weight standards available." (Sept. Tr. 1231:7-13 (Scandella).) And copolymer-1 was designed to imitate a protein, *i.e.,* myelin basic protein. (July Tr. 18:17-21 (Pinchasi); PTX 1 at col. 1:10-11.)

Moreover, globular proteins were recommended by the Superose 12 manufacturer, Pharmacia, as the calibration standards for the column. (Sept. Tr. 1231:7-13; 1235:20-1236:17 (Scandella); PTX 752 at TEV000953898.) As Dr. Scandella testified, "[s]ize exclusion chromatography is usually run using protein standards or other commercially available standards. So if I were running a protein or a polypeptide on size exclusion chromatography, I would use the globular protein standards that are recommended by the manufacturer as a starting point." (Sept. Tr. 1229:3-9 (Scandella).) Dr. Wall testified that the Pharmacia literature "was sort of the bible of size exclusion chromatography." (Sept. Tr. 1767:19-24 (Wall).)

If one of ordinary skill in the art in 1994 attempted to follow the teaching of the patents and calibrated the SEC column with commercially available proteins, one would not have known that the results obtained were four to five times higher than the results from other methods. (Sept. Tr. 1232:20-1233:1 (Scandella).) Even if one suspected that copolymer-1 had a different hydrodynamic volume or molecular shape from globular proteins, the proteins could still be appropriate SEC calibration standards, because one could have "simply reported the results as relative to globular protein standards," which is "widely done in size exclusion chromatography." (Sept. Tr. 1235:7-13 (Scandella).) [redacted]

[redacted]

449. Instead of globular proteins, in 1994, a person of skill in the art could have used self-standard calibration to accurately determine the peak molecular weight and molecular weight distribution (*e.g.*, the percentage of molecules between 2 and 20 kilodaltons or over above 40 kilodaltons) of a copolymer-1 sample. (Sept. Tr. (Grant) 1421:19-24, 1421:25-1422:8.)

Sandoz's Response:

To the extent Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is wrong, as explained above. And as Sandoz's experts explained at trial, the use of self-standards would not have enabled the claims. (Sandoz's Opening FFCOL ¶¶ 122-134.)

450. Self-standards are standards made from the same material as the sample being measured, and therefore would, by definition, have the same hydrodynamic volume-to-molecular weight characteristics as the sample being measured. (Sept. Tr. (Grant) 1399:23-1400:13.) Dr. Scandella spent significant time at trial discussing possible shapes of copolymer-1 (*see* Sept. Tr. (Scandella) 1202:23-1205:19, 1229:16-24), but that testimony was irrelevant to the use of self-standards.

Sandoz's Response:

Dr. Scandella, who has created self-standards that have been adopted by the World Health Organization and the National Institutes of Health, testified that "[t]he task of creating standards that match a sample as complicated as cop-1 is quite difficult and may take years." (Sept. Tr. 1206:9-11; 1250:7-1251:12 (Scandella).) He characterized it as a "major research project" and "major undertaking" that would not "yield a single well-defined product." (Sept. Tr. 1251:13-22; 1252:7-9 (Scandella).) Dr. Scandella further testified about the inherent variability of any copolymer-1 self-standards:

Q. In your opinion, would batch-to-batch consistency have been an issue for one of skill in the art trying to use copolymer-1 self standards?

A. Yes, I believe it would have.

Q. Why?

A. Because the synthetic procedure for making cop-1 had an inherent variability, so it was not possible to make two batches that were identical. So this means that this would be a problem for the synthesis of cop-1 markers.

(Sept. Tr. 1283:3-11 (Scandella).) [redacted] Thus, because the copolymer-1 self-standards would have variability from batch to batch, Dr. Scandella's testimony about the possible shapes of copolymer-1 in solution applies equally to self-standards.

451. Self-standard calibration had been thoroughly described in the scientific literature by 1994. For example, Billingham 1977 states that "[t]he most obvious method is to inject into the columns a series of monodisperse *standards of the polymer under test*" and that "[d]irect calibration with the polymer under test can be achieved by *using narrow distribution fractions of the polymer*." (PTX 514 at 210-11 (emphasis added); Sept. Tr. (Grant) 1414:8-1415:17.)

Sandoz's Response:

Copolymer-1 "is a complex substance and it cannot be even called a molecule, because it is actually a mixture of molecules. It's a mixture of copolymer-1 -- of copolymers having the four amino acids in the right molar ratio. But this mixture contains polymers with different sizes." (July Tr. 28:8-13 (Pinchasi).) According to Dr. Krull, copolymer-1 samples are "very heterogeneous." (DTX 1744 at TEV1017878 (emphasis in original).) Teva introduced no literature at trial and cites no literature here that describes how to create self-standards for a material as complex as copolymer-1. The Billingham quote expressly applies to *monodisperse* standards, not *polydisperse* mixtures such as copolymer-1. (Sept. Tr. 1298:25-1299:2

(Scandella).) In addition, the quote applies to "narrow distribution fractions," yet the narrowest fraction that could be obtained for copolymer-1 contains billions of molecules with different individual molecular weights and sequences. (Sept. Tr. 1193:24-1194:11; 1225:18-1226:1 (Scandella).) The very next sentence in the Billingham reference makes clear that the method of using "narrow distribution fractions" does not apply to polydisperse materials such as copolymer-1: "However, it is comparatively rare that a series of fractions will be available which cover a wide enough range of molar mass and are sufficiently monodisperse to satisfy equation 8.7." (PTX 514 at 211.) The referenced "equation 8.7" is found on the previous page and assumes that the various types of average molecular weight for the self-standard are equal, *i.e.*, Mp = Mn = Mw = Mv. (*Id.* at 210.) The undisputed evidence from trial is clear that these average molecular weights are not the same for copolymer-1. (Sept. Tr. 1196:18-23 (Scandella); 1484:22-1485:8 (Grant).) Thus, the method of using "narrow distribution fractions" cannot be used for copolymer-1, according to Teva's own reference.

Moreover, even if one made a copolymer-1 self-standard, "there was no good way to measure the molecular weight of a cop-1 standard in 1994." (Sept. Tr. 1251:25-1252:1 (Scandella).) That is because different molecular weight measurement methods yield very different results for a given copolymer-1 sample or standard, whether it be a whole batch or fractionated. (Sandoz's Opening FFCOL ¶¶ 123-132.) As Dr. Wall explained, attempting to make self-standards by fractionation only compounds that problem:

> If I took the copolymer-1 and fractionated it, now I'd end up with 10 or 20, however many samples I decided to take that now had to be analyzed by some other method to arrive at their molecular weight like ultracentrifuge and that still wouldn't resolve the problem.

(Sept. Tr. 1770:12-17; *see also id.* at 1820:12-24.)

452. There are two ways to obtain self-standards: one is to use as standards whole batches of the polymer of interest having different molecular weights ("whole polymer" self

standards), and the other is to use narrower fractions of the polymer sample of interest ("fractionated" self standards). (Sept. Tr. (Grant) 1399:23-1400:13.) Both are described in more detail below.

Sandoz's Response:

Using "whole polymer" or "fractionated" self-standards for copolymer-1 would not enable the claims. *See* Sandoz's Response to ¶ 451, which is incorporated by reference.

(a) Whole Polymer Self-Standards

453. The whole polymer self-standard method involves taking whole batches of the polymer of interest, each batch having a different molecular weight, and determining the molecular weights of the batches by independent (non-SEC) methods. (Sept. Tr. (Grant) 1401:9-11, 1418:7-15.)

Sandoz's Response:

Using "whole polymer" self-standards for copolymer-1 would not enable the claims. *See* Sandoz's Response to ¶ 451, which is incorporated by reference.

454. The whole polymer self-standard method was described in the literature well prior to 1994. (Sept. Tr. (Grant) 1401:9-11; 1418:7-1420:20; PTX 514 at 211; PTX 566 at 37.) For example, Billingham 1977 describes two different methods of calibration using whole polymer standards in a section entitled "Calibration with Whole Polymer." (PTX 514 at 212-13; Sept. Tr. (Grant) 1401:9-11.) Similar methods are also described in Barth 1991, which includes two sections entitled "Calibration Using Polydisperse Standards of Known Molecular Weight Averages" and "Calibration Using Standards of Known Molecular Weight Distribution." (Sept. Tr. (Grant) 1419:13-1421:3; PTX 566 at 37-44.)

Sandoz's Response:

Using "whole polymer" self-standards for copolymer-1 would not enable the claims. *See* Sandoz's Response to ¶ 451, which is incorporated by reference. In addition, the 1991 Barth article does not teach self-calibration for materials as complex as copolymer-1. The section entitled "Calibration Using Polydisperse Standards of Known Molecular Weight Averages" does not teach how to calibrate with self-standards of a complex material such as copolymer-1 whose measured molecular weights vary depending on the analytical method chosen. (DTX 566 at 37-41; Sandoz's Opening FFCOL ¶¶ 123-132.) The authors acknowledge that "even taking this

approach will provide a calibration curve of little practical use for complex polymers, if the shape of the local property distributions vary among the samples to be analyzed." (DTX 566 at 40.) As explained above, "this [copolymer-1] mixture contains polymers with different sizes," is "very heterogeneous," and the narrowest fraction that could be obtained contains billions of molecules with different individual molecular weights and sequences. (July Tr. 28:8-13 (Pinchasi); DTX 1744 at TEV1017878; Sept. Tr. 1193:24-1194:11; 1225:18-1226:1 (Scandella).)

The section entitled "Calibration Using Standards of Known Molecular Weight Distribution" does not apply to copolymer-1 either; it applies "[i]f the molecular weight distribution of a sample of the polymer of interest *is known*." (PTX 566 at 41 (emphasis added).) As explained above, the molecular weight distribution of the copolymer-1 sample would not be known; it would have to be measured by some independent method and the results would vary widely depending on the method used. (Sandoz's Opening FFCOL ¶¶ 123-132.)

455. In the case of copolymer-1, a person of skill in the art in 1994 could have made whole batches of copolymer-1 to use as self-standards, because the patents-in-suit teach how to make copolymer-1 of varying molecular weights. These batches could then be used as molecular weight standards. (PTX 1, col. 4:59-65; Sept. Tr. (Grant) 1401:19-1402:4; DTX 4022 (Varkony Dep.) at 252:4-13, 252:25-253:6, 257:17-22.) Dr. Sampson explained at trial that by varying the time and temperature of the HBr/acetic acid reaction step in the synthesis of copolymer-1, the molecular weight of the resulting copolymer-1 can be controlled. (Sept. Tr. (Sampson) 1641:6-1642:8; PTX 992 at 6-7.)

Sandoz's Response:

Copolymer-1 batches could not be used as standards to enable the claims. Whole batches of copolymer-1 would be "very heterogeneous" and would contain billions of molecules with different individual molecular weights and sequences. (DTX 1744 at TEV1017878; Sept. Tr. 1193:24-1194:11; 1225:18-1226:1 (Scandella).) The patents do not teach how to measure the molecular weights of such batches, and the evidence makes clear that regardless of how the

copolymer-1 batches were made, the measured molecular weights would vary widely depending on the analytical method chosen. (DTX 566 at 37-41; Sandoz's Opening FFCOL ¶¶ 123-132.)

(b) Fractionated Self-Standards

456. The fractionated self-standard method involves taking a mixture of the substance of interest and separating it into smaller portions, or fractions, that can be used as calibration standards. (Sept. Tr. (Grant) 187:8-14.)

Sandoz's Response:

Using "fractionated" self-standards for copolymer-1 would not enable the claims. *See* Sandoz's Response to ¶ 451, which is incorporated by reference.

457. The fractionated self-standard method had been fully described in the literature prior to 1994. (Sept. Tr. (Grant) 1400:16-18.) For example, Billingham 1977 states that "[d]irect calibration with the polymer under test can be achieved by using narrow distribution fractions of the polymer, prepared either by preparative fractionation or by preparative scale GPC." (Sept. Tr. (Grant) 1414:12-1418:6; PTX 514 at 211-12.)

Sandoz's Response:

Using "fractionated" self-standards for copolymer-1 would not enable the claims. *See* Sandoz's Response to ¶ 451, which is incorporated by reference.

458. Fractionation of copolymer-1 into smaller portions of varying molecular weight is described in the patents-in-suit. The patent describes fractionation of copolymer-1 by running a sample through an SEC column and collecting the fractions as they exit the column. (PTX 1, col. 2:57-3:2; Sept. Tr. (Grant) 1400:16-1401:8, 1402:5-9; Sept. Tr. (Scandella) 1322:20-1324:7.) Fractionation was well known in the art in 1994. (Sept. Trial Tr. (Grant) 1400:16-18; (Zeiger) 866:11-20; 894:23-895:14.)

Sandoz's Response:

Neither the patents nor the prior art teach how to overcome the problem of the inherent variability that would be present in even the smallest fraction of copolymer-1, which undermines the utility of any copolymer-1 self-standards. *See* Sandoz's Response to ¶ 450, which is incorporated by reference. Because of this variability, the FDA observed that copolymer-1 self-standards "may only serve for estimation of the relevant molecular weight values." (DTX 3507

at TEV000213922.) Teva itself reached the same conclusion in 1995, observing that for SEC, "the sample molecular weight distribution and the calculated molecular weight averages are at best an approximation relative to the standard used. Copolymer-1 markers having the same structure and conformation have been prepared and are employed for *estimation* of molecular weights." (DTX 3509 at TEV001116165 (emphasis added).) Teva even changed its molecular weight specifications because of this issue: "The term determination with respect to molecular weight was changed to estimation, *in response to FDA's expressed doubts about the accuracy furnished by a calibration based on glatiramer acetate markers*." (DTX 3507 at TEV000213922 (emphasis added); Sept. Tr. 1523:14-1524:2 (Grant).)

Moreover, "there was no good way to measure the molecular weight of a cop-1 standard in 1994." (Sept. Tr. 1251:25-1252:1 (Scandella).) That is because different molecular weight methods yield very different results for a given copolymer-1 sample or standard. (Sandoz's Opening FFCOL ¶¶ 123-132.)

459. Each of the resulting fractions will have a different molecular weight, which can be independently measured so that the fractions can be used as calibration standards. (Sept. Tr. (Grant) 1402:10-24.)

Sandoz's Response:

See Sandoz's Response to ¶ 458, which is incorporated by reference.

(c) Known Methods in 1994 Yielded Variable Results for the Molecular Weight of Copolymer-1 Self-Standards

460. Once self–standards—whether whole or fractionated—are made, a person of skill in the art would have measured their molecular weights by an independent (non-SEC) method. (Sept. Tr. (Grant) 205:6-10, 1402:10-18.) At least some of these methods are known as absolute molecular weight methods. (Sept. Tr. (Grant) 1416:14-17.)

Sandoz's Response:

Although certain methods are considered to provide "absolute" molecular weights, "that doesn't mean that every measurement by all of these techniques gives you an absolute molecular

weight. All of these methods are subject to limitations and complication, especially when dealing with complex molecules….[l]ike copolymer-1." (Sept. Tr. 1207:21-1208:7 (Scandella); 1763:5-15 (Wall).) "[T]here is no assurance that any one technique is going to give absolute values for the cop-1 molecular weight." (Sept. Tr. 1261:21-22 (Scandella).) And the evidence at trial established that when Teva itself used different methods to measure its copolymer-1 standards, it obtained different values. (*See* Sandoz's Opening FFCOL ¶¶ 123-132.) Thus, Teva made clear that which analytical technique was used to measure the molecular weight of the copolymer-1 standards should be "explicitly stated." (DTX 3137 at TEV000290820.)

461. The methods available in 1994 for measuring the molecular weights of self-standards included, *e.g.*, multi-angle light scattering, viscometry (a.k.a. "viscosimetry"), ultracentrifugation, and mass spectrometry. (Sept. Tr. (Grant) 1402:19-1403:2; Sept. Tr. (Scandella) 1318:2-8.)

Sandoz's Response:

Disputed to the extent this list purports to be exhaustive. Other methods were available for this purpose, including osmometry. (Sept. Tr. 1258:22-25 (Scandella).) Moreover, these different methods yield different molecular weight results for copolymer-1. (*See, e.g.*, Sept. Tr. 1259:13-1260:11 (Scandella); DTX 3581 at 12.)

(d) It Was Not Possible in 1994 to Create a Single Calibration Curve for Copolymer-1 Self-Standards

462. Once the molecular weights of the self-standards had been measured, a person of skill in the art would use them to calibrate the SEC column by running them through the column, recording the times at which they exit the column, and then creating a calibration plot to correlate their molecular weights to their retention times. (Sept. Tr. (Grant) 1402:10-18.)

Sandoz's Response:

As Dr. Wall explained at trial, even if one were able to make copolymer-1 self-standards, "they still would have been faced with the insurmountable problem in terms of setting up the molecular weight calibration of determining the molecular weight method that would be used to

characterize your standards." (Sept. Tr. 1819:21-1820:8.) And, "[a]s Teva showed, you need to use many different methods and make choices about which method and which type of molecular weight average to use," because the measured molecular weight of copolymer-1 varies depending on the method that is used. (Sept. Tr. 1252:1-3; 1254:1-3 (Scandella).) Dr. Grant agreed:

> Q. But depending on the method used to measure the molecular weight of the self-standard you may get a different type of molecular weight, right?
>
> A. You may.

(Sept. Tr. 1487:21-24 (Grant).) Dr. Pinchasi also agreed:

> Q. Now you understand that a material that would be measured at 14,000 kilodaltons with one method can be about 11,000 with another method; correct?
>
> A. I understood from analytical chemists, although I'm not a chemist and I cannot explain why is this, that different methods can provide different results.
>
> Q. And it was your understanding at the time that it's not easy to compare side by side data from different methodologies, correct?
>
> A. It's not easy. You have to understand very well what you are measuring.

(July Tr. 277:13-23 (Pinchasi); *see also id.* at 254:23-25.)

Dr. Pinchasi further testified that "there was no way to really control the molecular weight of the final [copolymer-1] product. You did -- you thought you did exactly the same thing each time, but you got molecular weight with very different -- very different molecular weights at the end of the day." (July Tr. 38:21-25 (Pinchasi).)

Documents introduced at trial show that one would have obtained a wide range of molecular weight results for copolymer-1 self-standards, depending on the analytical method chosen. For example, a table in a November 1995 Teva document lists 15 copolymer-1 markers and their average molecular weights obtained by ultracentrifugation, viscosimetry and MALLS. (DTX 3509 at TEV001116167; Sept. Tr. 292:6-23 (Grant).) Depending on the method that was

used, the molecular weight for a given standard varied by up to 2,100 daltons (marker 02095 [5,800 - 7,900 daltons]) in the lower end of the molecular weight range and up to 3,000 daltons in the upper end of the range (marker BD-402 [22,200-25,200 daltons]). (DTX 3509 at TEV001116167.)

Additional molecular weight data for these same markers confirms the problem. An August 1995 document lists the Mw and Mn MALLS results for these same 15 markers, and another document lists additional Mw and Mn results from several other molecular weight analyses on these same markers. (DTX 1699; Sept. Tr. 1527:4-1528:19 (Grant); DTX 1642 at TEV001013041, TEV001013087; Sept. Tr. 1528:23-1529:24 (Grant).) When all of these data are considered, even greater variation is revealed in the estimated molecular weights of each copolymer-1 marker. For marker 02095, for example, there was a variation of nearly 5,000 daltons for the Mn values (5,200 - 10,100 daltons) and a variation of 9,000 daltons for the Mw values (5,800 - 14,800 daltons). (DTX 1699 at TEV000950015; DTX 1642 at TEV001013041.) The variation was even more pronounced for higher molecular weight markers. The Mw value of marker BD-402, for example, varied from 22,200 to 48,900 daltons depending on the analysis selected. (*Id.*)

Because the molecular weight results for copolymer-1 self-standards depend on the analytical method used, there are multiple ways to calibrate the SEC column, with each calibration providing a different result. (DTX 3581 at 16; Sept. Tr. 1272:5-1273:7 (Scandella).) Dr. Scandella so testified:

> Q. Just briefly, in your opinion, if one uses copolymer self standards, will the calibration curve be the same regardless of the analytical method chosen to determine the molecular weights of those standards?
>
> A. No. I think we've seen that it will not.

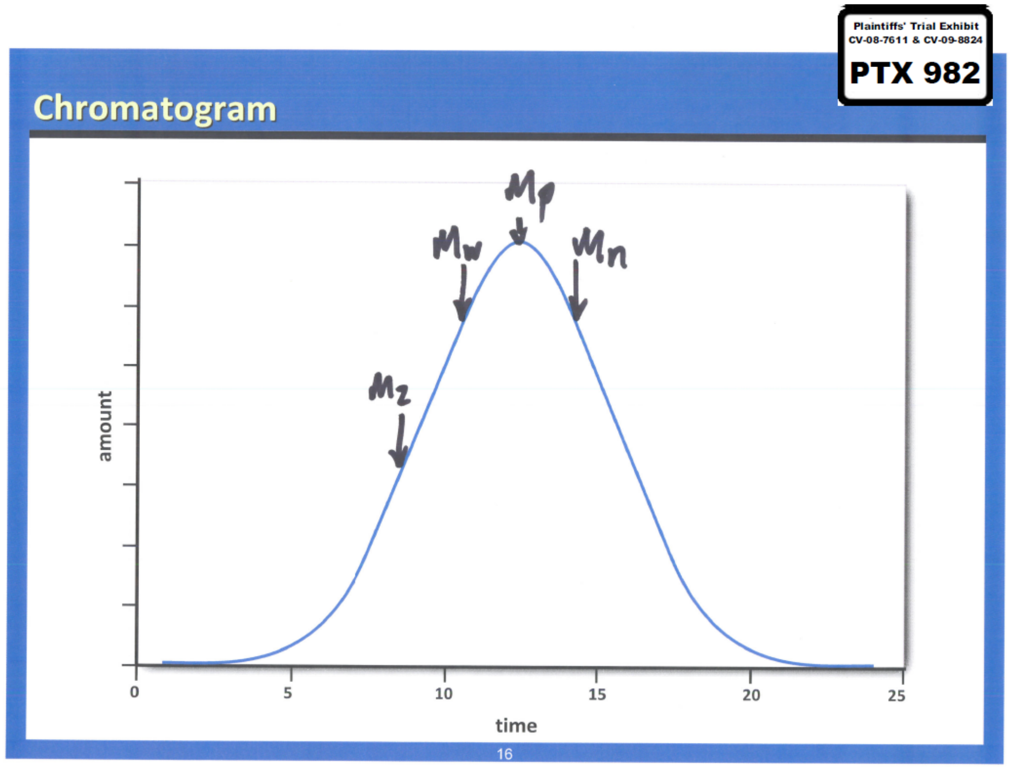
(Sept. Tr. 1272:6-10.) And as Dr. Wall explained:

> [W]hen you use even absolute molecular weight determinations on the same copolymer-1 batch, you get a range of values from 4,000 to 11,000. So any one of those absolute molecular weight determinations could be used to calibrate your standards and determine their molecular weight. That being the case, a person of ordinary skill would not know unless you told them in the patent how the molecular weights had been determined and what the standards were like. So essentially, he would be in the dark.

(Sept. Tr. 1818:18-1819:1 (Wall).) As a result, "[y]ou'd get a very different calibration curve." (Sept. Tr. 1819:2-14 (Wall).)

463. If self-standards were used for calibration, their average molecular weights could vary depending on the absolute method used to determine the molecular weight of the standard (*e.g.*, light scattering could measure a weight average molecular weight, while osmometry could measure a number average molecular weight). The different average molecular weight values provided by the various techniques would correspond to different retention times along the chromatogram for the sample. (Sept. Tr. (Grant) 1404:7-20; Sept. Tr. (Scandella) 1326:19-1327:16.) For example, if these various molecular weights are mapped out on a chromatogram shaped as in PTX-982, the z-average molecular weight (Mz) would come out first (because it is the highest value and larger molecules exit the size exclusion column first), then the weight average molecular weight (Mw), followed by the peak average molecular weight (Mp) at the peak of the chromatogram, and then the number average molecular weight (Mn), after the peak (because it is generally the smallest of the "average" values), as shown below. (PTX 982; Sept. Tr. (Scandella) 1325:2-1326:18; Sept. Tr. (Grant) 1404:23-1405:13.)

Figure 21



Sandoz's Response:

Sandoz does not dispute the general order of the average molecular weights shown in PTX 982. Sandoz does dispute the remainder of paragraph 463 as misleading and incomplete. If self-standards were used for calibration, it is not merely the type of molecular weight average (Mz vs. Mw vs. Mn) that would vary depending on the method chosen. Rather, the molecular weight values themselves would vary across methods, *even for the same type of average*. *See* Sandoz's Response to ¶ 462 and Sandoz's Opening FFCOL ¶¶ 126-130, which are incorporated by reference.

In addition, while it is true that the different types of average molecular weight for a given sample (Mz vs. Mw vs. Mn) would correspond to different retention times along the chromatogram for the sample, when there is more than one value for each of these averages (*e.g.*,

Mn = 4,000 by MALDI-TOF and Mn = 10,000 by MALLS), one cannot make a correction to accommodate those discrepancies. (DTX 3137 at TEV000290819; Sept. Tr. 1293:15-21; 1295:10-13 (Scandella).) Instead, one is faced with a choice of which value to use, recognizing that the calibration curves will be different depending on the choice that is made. (Sept. Tr. 1272:5-10 (Scandella); 1803:7-14 (Wall).) For one of skill in the art attempting to reproduce the copolymer-1 of the claimed invention, one must know which method was used by the patentees to determine the molecular weights of the self-standards. (Sept. Tr. 1253:4-12 (Scandella).) Only with that information can one make the same choice that the patentees made and attempt to obtain a comparable calibration curve. (Sept. Tr. 1271:10-16; 1295:10-13 (Scandella).) Making a different choice could lead to "a very different calibration curve," with molecular weight results that are "ten-fold too low." (Sept. Tr. 1819:2-14 (Wall);1259:1-6; 1295:10-13 (Scandella).)

464. The only technical difficulty with self standards identified by Sandoz's expert Dr. Scandella is that the different average molecular weight values measured by the different absolute measurement methods for the standards would result in different calibration curves, which would in turn lead to different determined molecular weights for the sample depending on which calibration curve was used. (Sept. Tr. (Scandella) 1272:3-25; DTX 3581 at 16.) On cross-examination, however, Dr. Scandella admitted that the demonstrative exhibit he presented to the Court to explain this alleged discrepancy did not accurately depict the time associated with the measured molecular weight of the standard (*i.e.*, the time along the chromatogram for the self standard that would correlate with the measured average molecular weight for the standard). Although he agreed that each different type of measured average molecular weight for a standard would be associated with a *different retention time*, he admitted that his demonstrative depicted all of the different average molecular weights as being associated with the *same retention time*. (Sept. Tr. (Scandella) 1326:24-1327:21.) When confronted with this discrepancy, Dr. Scandella testified that his demonstrative was "not intended to be actual data." (Sept. Tr. (Scandella) 1327:24-25.)

<u>*Sandoz's Response:*</u>

Dr. Scandella testified at length about the problems with using copolymer-1 self-standards for SEC calibration, and his testimony was not limited in the manner suggested by

Teva. *See* Sandoz's Responses to ¶¶ 450-451 and Sandoz's Opening FFCOL ¶¶ 122-133, which are incorporated by reference. Dr. Wall testified similarly:

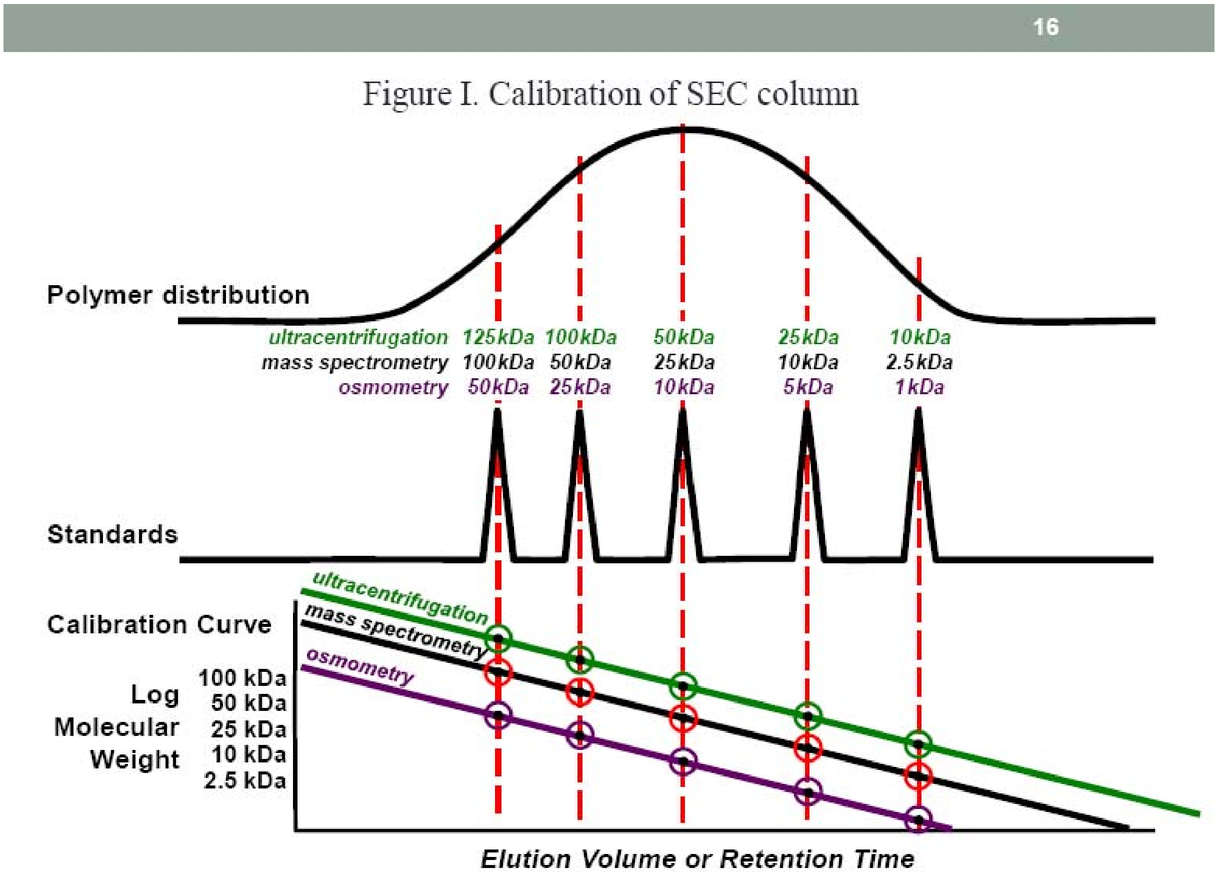
> Q. And, in your opinion, is the lack of enablement -- is the lack of enablement problem with the patents related solely to the type of molecular weight average used to measure self standards?
>
> A. No, it's not a matter of whether you're looking at Mw or Mn or Mz or Mp or Mv, whatever. All of those values, for example, data we didn't look at, showed that with different determinations which allow you to get let's say Mn and Mw, gave you different results. So this was not a matter of applying some correction. And as far as I know, Teva never applied any corrections to any of these.

(Sept. Tr. 1808:24-1809:9.)

Teva is incorrect that slide 16 from Dr. Scandella's demonstrative presentation, DTX 3581, "did not accurately depict the time associated with the measured molecular weight of the standard" and is incorrect that Dr. Scandella testified to that effect. In fact, Dr. Scandella specifically testified that there was nothing inaccurate about the slide:

> Q. Is there anything incorrect about this slide?
>
> A. As it stands, no.

(Sept. Tr. 1338:6-7.) It is Teva who misunderstands or deliberately misconstrues what is depicted in slide 16, which is reproduced below.



(DTX 3581 at 16.) According to Dr. Scandella, slide 16 illustrates that "different molecular weight values applied to the same standard would create different calibration curves, and that the molecular weights measured from the calibration curves would depend on which curve you used." (Sept. Tr. 1338:1-5.) Teva misrepresents Dr. Scandella's testimony by stating that "he admitted that his demonstrative depicted all of the different average molecular weights as being associated with the same retention time." When asked this very question, Dr. Scandella disagreed:

> Q. It has a time, and you've applied all those average molecular weights at the very same time, right?

> A. Well, this is an example for illustration only. It's not intended to be actual data.

(Sept. Tr. 1327:22-25.) Despite the fact that the slide "is an example for illustration only" and "not intended to be actual data," Teva attempts to graft on Mn and Mw data that are not part of the slide. (Sept. Tr. 1326:24-1327:25 (Scandella).) There is no indication on the slide that the molecular weight values for osmometry, mass spectrometry and ultracentrifugation are Mn or Mw values and not Mp values. In fact, the listed values line up with the chromatogram peaks, which indicates that, had these been actual data, any correction to obtain the Mp values was *already applied*. (DTX 3581 at 16.)

465. Even though he testified regarding the differences between types of measured average molecular weight for self-standards, Dr. Scandella admitted that he does not have any experience working with polydispersed mixtures of polypeptides such as copolymer-1. (Sept. Tr. (Scandella) 1298:25-1299:7.) Dr. Scandella testified at his deposition that he had never done any SEC analysis of synthetic polypeptides. (Sept. Tr. (Scandella) 1299:20-1300:7.) Further, Dr. Scandella has no publications concerning the molecular weight of a protein using SEC. (Sept. Tr. (Scandella) 1300:8-12.)

<u>Sandoz's Response:</u>

Dr. Scandella explained at trial that he has experience with SEC analysis of synthetic polypeptides. (Sept. Tr. 1299:8-12.) Dr. Scandella explained that "[i]t's not common to make polydispersed mixtures of polypeptides." (Sept. Tr. 1299:5-6.) Dr. Wall agreed:

> Q. Just to make sure I'm clear. You've never used size exclusion chromatography to determine the average molecular weight of a mixture of polypeptides like copolymer-1, right?
>
> A. As far as I know up to the 1995 time frame, no one was doing that except Teva and their contractors.

(Sept. Tr. 1760:9-13.) Indeed, Teva's own expert, Dr. Grant, testified that he had no experience with copolymer-1 prior to this case. (Sept. Tr. 271:5-14.) In addition, Dr. Scandella testified that he has presented at meetings the results of his research involving the molecular weight of a protein using SEC. (Sept. Tr. 1300:8-12.) Moreover, Dr. Scandella used size exclusion

chromatography in every project that he worked on at Chiron, where he was recognized as an expert in SEC by Pharmacia, the manufacturer of the Superose 12 column. (Sept. Tr. 1180:4-13; 1181:14-1183:14 (Scandella).) Dr. Scandella has performed "at least 10,000" SEC analyses in his career. (Sept. Tr. 1181:11-12 (Scandella).)

466. Dr. Grant explained why Dr. Scandella's demonstrative exhibit was inaccurate. (Sept. Tr.(Grant) 1403:14-1404:20.)

Sandoz's Response:

Sandoz does not dispute that Dr. Grant purported to explain why he believed Dr. Scandella's demonstrative exhibit was inaccurate, but Sandoz disputes that Dr. Grant's explanation was correct or that there is anything inaccurate about the demonstrative. Dr. Grant's explanation is incomplete and misleading. In particular, Dr. Grant argued that the weight average values (ultracentrifugation) would shift in one direction and the number average values (osmometry) would shift in the opposite direction such that the different calibration curves "would end up becoming the same calibration curve." (Sept. Tr. 1405:14-25 (Grant).) But Dr. Grant neglected to address the fact that there are *three* calibration curves on Dr. Scandella's demonstrative, not *two*. (DTX 3581 at 16.) Dr. Grant failed to explain what would happen to the mass spectrometry curve. The evidence in the record shows that mass spectrometry yields a number average molecular weight. (DTX 3137 at TEV000290819.) Dr. Grant provided no explanation whatsoever as to how two calibration curves that are both based on number average molecular weight (osmometry and mass spectrometry) could "end up becoming the same calibration curve." (Sept. Tr. 1405:14-25 (Grant).)

The evidence in the record establishes that molecular weight results for copolymer-1 standards are highly variable even among methods that yield the same type of molecular weight average. (*See* Sandoz's Opening FFCOL ¶¶ 127-129.) For example, the molecular weight of

copolymer-1 sample R.S. 03494 was Mn = 4,000 daltons when analyzed by MALDI-ToF but was Mn = 10,000 daltons when analyzed by MALLS. (DTX 3137 at TEV000290819.) As another example, the molecular weight of copolymer-1 batch 13 was Mn = 638 daltons when analyzed by osmometry but was Mn = 7,000 daltons when analyzed by other methods. (DTX 1269 at TEV001090158.) As yet another example, Teva obtained highly discrepant Mn values and highly discrepant Mw values for a set of 15 copolymer-1 self-standards that it analyzed by multiple methods. (DTX 3509 at TEV001116167; DTX 1699 at TEV000950015; DTX 1642 at TEV001013041, TEV001013087.) For marker 02095, there was a variation of nearly 5,000 daltons for the Mn values (5,200 - 10,100 daltons) and a variation of 9,000 daltons for the Mw values (5,800 - 14,800 daltons). (DTX 1699 at TEV000950015; DTX 1642 at TEV001013041.) The variation was even more pronounced for higher molecular weight markers. The Mw value of marker BD-402, for example, varied from 22,200 to 48,900 daltons depending on the analysis selected. (*Id.*) Dr. Grant's simplistic analysis does not account for variation of this nature.

467. As Dr. Grant testified, despite the potential difference in the average molecular weight (and hence the corresponding retention time) obtained using different absolute measurement techniques, it was well known in 1994 how to appropriately apply the different measured average molecular weights obtained using different methods to get an appropriate calibration curve that would provide an accurate molecular weight. (Sept. Tr. (Grant) 327:9-16.) The process of obtaining a single accurate calibration curve from the measured molecular weights of self-standards was described extensively in the literature. (Sept. Tr. (Grant) 1403:3-13.) The literature provided numerous examples of procedures that could have been used to resolve calibration curves produced by different absolute molecular weight measurement techniques into a single calibration curve. (Sept. Tr. (Grant) 1408:25-1409:4.)

<u>*Sandoz's Response*</u>:

None of the literature cited by Dr. Grant teaches or even suggests that it is possible to resolve discrepant calibration curves into a single calibration curve when the discrepancies include different Mn values or different Mw values for the same sample, as is the case for

copolymer-1. Nor did Dr. Grant testify that resolution to a single curve in such circumstances could be accomplished. *See* Sandoz's Response to ¶ 466, which is incorporated by reference.

468. For example, for fractionated self-standards, Billingham 1977 describes ways to calculate the peak molecular weight of the self standards such that it can be accurately applied at the peak time. Dr. Grant explained that this means that "since a number average or a weight average is not going to have a time associated with it that's equal to the peak, you have to do some calculation or adjustment to be able to find what the accurate molecular weight at the peak." (Sept. Tr. (Grant) 1414:22-1417:3; PTX 514 at 211.) Dr. Grant also explained that a paper from the early 1970s cited by Billingham 1977 describes "several different types of methods that had already been developed by that time to do this adjustment, this calculation of the peak molecular weight from other types of average molecular weights" and that mathematical treatments that could be used to convert number average or weight average molecular weights into peak molecular weights were described in the literature in 1994. (Sept. Tr. (Grant) 1417:4-1418:6; PTX 514 at 211.)

Sandoz's Response:

See Sandoz's Responses to ¶¶ 466 and 467 which are incorporated by reference.

469. Additionally, Barth 1991 describes a variety of methods for generating calibration curves using polydisperse self-standards. (PTX 566 at 37-41.) Dr. Grant explained that Barth 1991 describes "a process that allows you to determine the accurate molecular weight at the peak for constructing a valid calibration curve" because "Mn and Mw are average molecular weights that can be determined by absolute methods" and "they do not correspond to molecular weights at the same time as the peak." (Sept. Tr. (Grant) 1419:13-1421:3; PTX 566 at 37.)

Sandoz's Response:

See Sandoz's Responses to ¶¶ 466 and 467 which are incorporated by reference. In addition, as explained above, the 1991 Barth article does not teach self-calibration for materials as complex as copolymer-1. *See* Sandoz's Response to ¶ 454, which is incorporated by reference.

470. Dr. Grant further explained that Billingham 1977 and Barth 1991 represent only a very small part of the literature that was available in 1994 describing the processes for generating valid calibration curves and that "in fact there are well described and valid and effective methods to take calibration curves that may be constructed from different types of average molecular weights and resolve them into a single calibration curve, so that in fact in the end you only had a single valid calibration curve, and gives you an accurate molecular weight at the peak of your measuring." (Sept. Tr. (Grant) 1421:4-18.)

Sandoz's Response:

See Sandoz's Responses to ¶¶ 466 and 467 which are incorporated by reference.

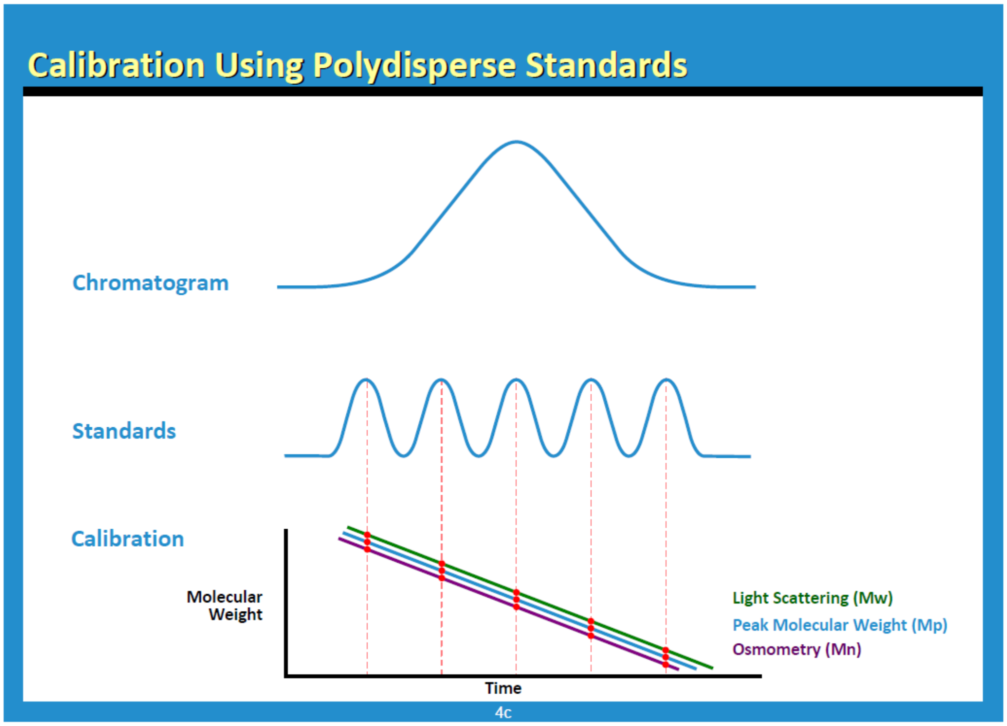
471. Dr. Grant presented a demonstrative to explain this technique described in the literature for applying different average molecular weight results from different techniques to generate a single valid calibration curve. (Sept. Tr. (Grant) 1406:1-1409:11; PTX 990 at 4a-i.) Dr. Grant presented an illustrative chromatogram of five broad self-standards, such as copolymer-1 self-standards, and a calibration curve based on the peak molecular weight times of the self-standards. (Sept. Tr. (Grant) 1406:1-17; PTX 990 at 4a.)

Sandoz's Response:

Sandoz does not dispute that Dr. Grant presented a demonstrative that purported to explain this technique, but Sandoz disputes that the technique is applicable to copolymer-1, for at least the reasons stated in Sandoz's Responses to ¶¶ 466 and 467 which are incorporated by reference.

472. Dr. Grant explained that one would get different calibration curves if the different average molecular weights for the standards obtained through different absolute molecular weight measurement techniques were assigned to the same, *e.g.*, peak, retention time. This occurs because, as shown in his example, one technique, light scattering, gives a higher average value (a "weight" average (Mw)) than the peak average value, while a second technique, osmometry, gives a lower average value (a "number" average (Mn)) than the peak average value, but the weight average and number average values are being (erroneously) applied at the *same time* (the "peak" time). (Sept. Tr. (Grant) 1406:18-25,1407:7-13; PTX 990 at 4c.)

<u>Figure 22</u>



<u>Sandoz's Response:</u>

Dr. Grant's simplistic demonstrative fails to explain how one would account for a third calibration curve, such as mass spectrometry (Mn) or ultracentrifugation (Mw), that is different from the other curves. Dr. Grant cited no literature that explained how to resolve multiple calibration curves derived from analytical methods that yield the same type of molecular weight average, such as two Mn methods or two Mw methods. As explained above, actual data for copolymer-1 indicate highly variable Mn values and highly variable Mw values for the same sample, depending on the analytical method chosen. *See* Sandoz's Response to ¶¶ 466, which is incorporated by reference.

473. Dr. Grant explained that an adjustment was described extensively in the pre-1994 literature that addressed this issue. This adjustment would allow the different average molecular weights to be applied at the correct time. Such an adjustment—calculating the molecular weight of the standard at the peak so that it could be accurately applied at the peak time or appropriately applying the measured average molecular weight of the standard at its appropriate time—would

cause the theoretically different calibration curves to be merged into a single accurate calibration curve. (Sept. Tr. (Grant) 1406:25-1407:6; PTX 990 at 4c-i.)

<u>*Sandoz's Response:*</u>

See Sandoz's Response to ¶¶ 472, which is incorporated by reference. Moreover, there is no evidence that Teva applied any such adjustment or correction, so one would not know whether a correction was even applicable to the claimed molecular weights. (Sept. Tr. 1808:24-1809:9 (Wall).) Although Dr. Grant testified that he saw a document where Teva attempted to apply a conversion, neither Dr. Grant nor Teva has identified any such document or suggested that Teva actually used a conversion. (Sept. Tr. 1494:23-1495:11.) No mention of any conversion is made in Teva's SI-15247 protocol, which outlines the procedures for SEC calibration using copolymer-1 self-standards whose molecular weights were determined by MALLS. (DTX 1701.)

474. Dr. Grant demonstrated how a calibration curve based on weight average molecular weight (which is a larger value than the peak molecular weight value and therefore corresponds to a time to the left of the peak) of self standards could be adjusted. (Sept. Tr. (Grant) 1407:20-1408:8; PTX 990 at 4d.) Similarly, Dr. Grant demonstrated how a calibration curve based on number average molecular weight value (which is smaller than the peak molecular weight value and therefore corresponds to a time to the right of the peak) of self-standards is adjusted. (Sept. Tr. (Grant) 1408:9-24; PTX 990 at 4f.) Dr. Grant testified without rebuttal that the adjustment would, in effect, move the weight average molecular weights to earlier times, *i.e.*, to the left (because larger molecules come out of the size exclusion column before smaller molecules). This would have the effect of sliding the light scattering calibration curve to the left. (Sept. Tr. (Grant) 1406:18-1407:6.) Similarly, the adjustment would have the effect of moving the osmometry curve to later times, *i.e.*, to the right. (Sept. Tr. (Grant) 1407:7:1408:24.) The adjustments are shown in the graphs below:

Figure 23

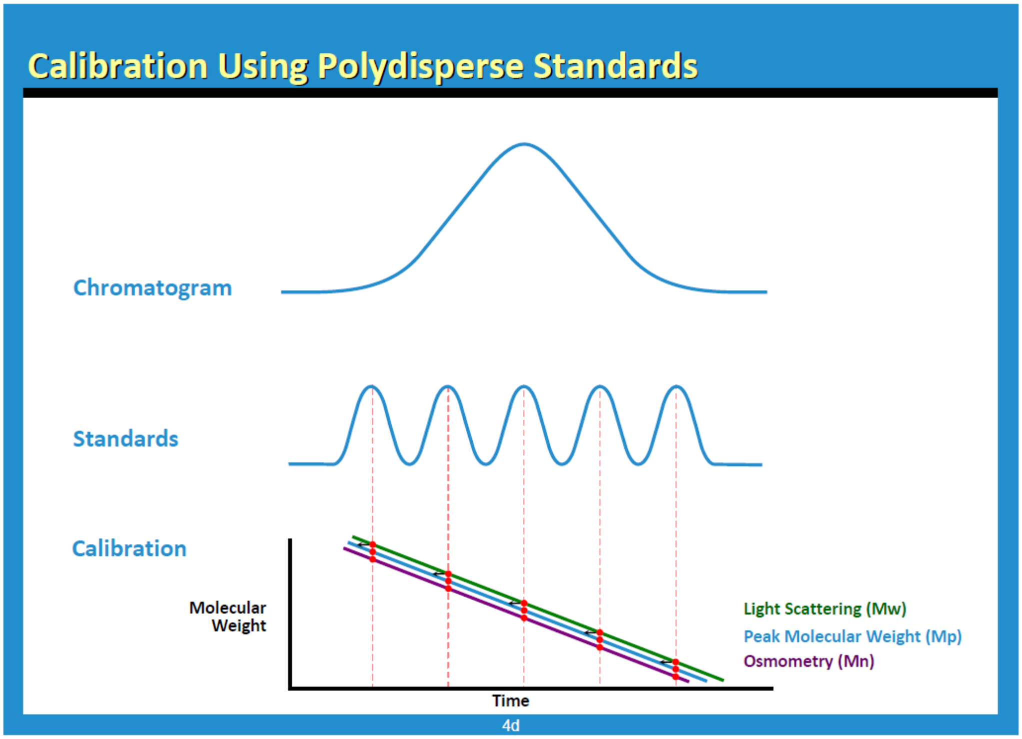
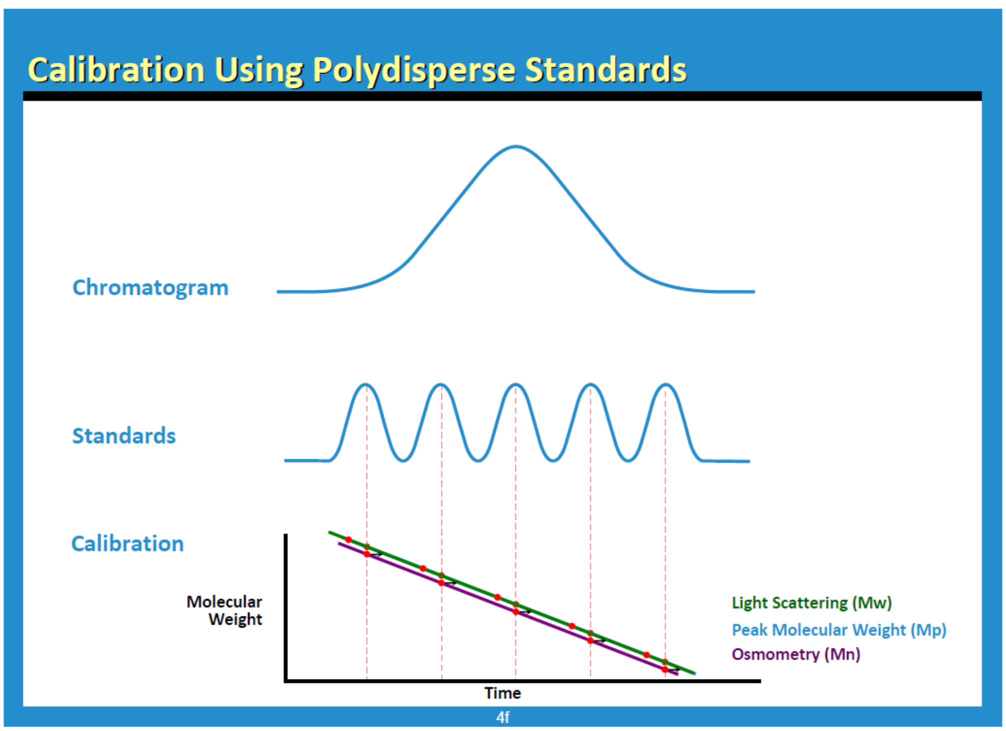


Figure 24



<u>*Sandoz's Response:*</u>

See Sandoz's Response to ¶¶ 466, which is incorporated by reference. In addition, Dr. Grant's demonstrative fails to explain how one would resolve calibration curves where the Mw curve is lower than the Mn curve or where those curves are the same. Such a scenario is supported by actual copolymer-1 data, as shown below:

SAMPLE	Mw
BD 80-1	4,000
BD 83-1	21,500
BD 114	31,300
BD 403	14,300
BD 420	5,200
BD 422	15,800
00895	9,300
01195	10,100
01495	7,600
01695	8,400
01795	7,400
02095	5,800
50595	7,900
50695	8,700
SD 1710	5,100
SD 1728	3,200
BD 402	22,200
BD 515	17,200

Sample	Mn
Albumin egg	
Trypsin inhibitor	
Lysozyme	14700
R-Nase	
Albumin,bovine	
02095	10100
00895	11300
01495	10700
01195	10000
01695	8800
01795	9400
50595	10700
50695	11200
BD-114	39300
BD-402	24500
BD-403	16200
BD-422	17000
SD-1710	7500
BD-420	7000
BD-515	14800
03494	13700
03294	

(DTX 1699 at TEV000950015; DTX 1642 at TEV001013041.) As can be seen from the data, the Mw values for 13 out of 15 markers are lower than the Mn values from a different molecular weight analysis of the same markers. Under Dr. Grant's theory, the lower Mw curve and the higher Mn curve would shift away from each other rather than towards each other, because the Mw curve would shift further "to the left" and the Mn curve would shift further "to the right."

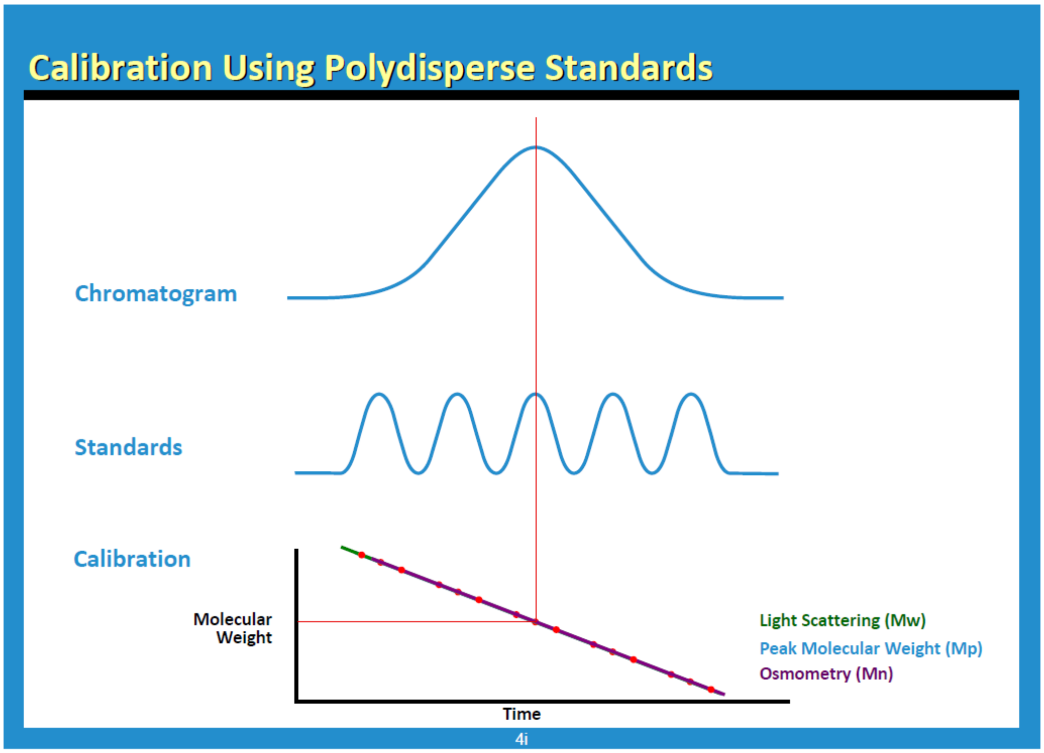
Thus, the corrections to a "peak" curve would not be the same, and different calibration curves would remain.

475. As explained by Dr. Grant, "the end result is that all three calibration curves become one." (Sept. Tr. (Grant) 1408:17-18.) Dr. Grant further explained how the single calibration curve could be used to obtain an accurate molecular peak molecular weight for a sample:

> At the end of the day, what this means is that you in fact do not have three different calibration curves from which you have to choose which one to use. You in fact have only a single calibration curve that gives you only a single accurate value for the peak of the chromatogram. . . . You locate the time of the peak, come down, find that time on your calibration curve, and you go over and read the molecular weight.

(Sept. Tr. (Grant) 1409:5-16; PTX 990 at 4i.)

Figure 25



Sandoz's Response:

Dr. Grant never explained how the three calibration curves in Dr. Scandella's demonstrative could "become one." Even assuming that any correction to obtain the Mp values was not already applied to those curves, two of the curves reflect techniques that yield number average molecular weights, osmometry and mass spectrometry, yet those two Mn curves are far apart. (DTX 3137 at TEV000290819; DTX 1269 at TEV00010901158; DTX 3581 at 16.) Dr. Grant proposed no procedure by which to resolve two discrepant Mn curves (or two discrepant Mw curves).

Dr. Grant's analysis completely ignores the evidence in the record that the molecular weight values obtained for copolymer-1 self-standards vary tremendously depending on the method chosen; that variation includes discrepancies of thousands of daltons in the Mn values and in the Mw values for the same samples. (Sandoz's Opening FFCOL ¶¶ 127-129.) Dr. Grant did not even attempt to account for such differences nor did he suggest that any literature teaches how to deal with such differences. As Sandoz's experts explained at trial, the only way to deal with such discrepant molecular weight values would be to follow the precise path that the patentees took in calibrating the SEC column for copolymer-1. (Sept. Tr. 1295:10-13 (Scandella); Sandoz's Opening FFCOL ¶ 118.) Because the patents do not disclose that path, one of skill in the art would not know how to reproduce the copolymer-1 having the claimed molecular weights. (Sandoz's Opening FFCOL ¶¶ 117-120.) Dr. Wall explained further:

> Q. So would the correction procedure that Dr. Grant suggested be used, would that enable one of skill in the art to practice the patent, given just the disclosure of using a superose 12 column?
>
> A. No, because that would wouldn't tell you what the standards were to start with, on which you had applied a correction.
>
> Q. And would it tell you what analytical methods were measured or used to measure those standards?

A. No, that's not stated in the specification either.

(Sept. Tr. 1809:14-22.)

476. Dr. Scandella agreed that techniques for correctly applying the measured average molecular weights of the standards at the correct retention time could have been available in 1994, but that he had not "looked at that recently." (Sept. Tr. (Scandella) 1328:7-16.)

Sandoz's Response:

Dr. Scandella disputed that such techniques were even relevant to his demonstrative:

Q. You didn't look into whether or not, before 1994 it was described in the literature how to appropriately apply those weight average and number average values?

A. Well, that's a separate question from what we're looking at here. This is talking about how you calibrate the column.

(Sept. Tr. 1328:20-24.) Dr. Scandella also specifically testified that there was nothing inaccurate about his demonstrative. (Sept. Tr. 1338:6-7.)

(e) Teva Attempted to Use Copolymer-1 Self-Standards to Determine the Molecular Weight of Copolymer-1 in 1987 But Abandoned Them

477. By August 1987, very early in its involvement in the copolymer-1 project, Teva had developed an effective method for accurately determining the molecular weight of copolymer-1. (Sept. Tr. (Grant) 1450:15-18, 1451:23-25, 1462:18-23; DTX 3275.)

Sandoz's Response:

The term "accurately" is not defined in this paragraph nor in the cited testimony and is not part of the Court's claim construction for the "molecular weight" limitations. To the extent Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is wrong. As Sandoz's experts testified, "SEC doesn't yield absolute molecular weights. It's not an absolute measurement method. So one wouldn't assume that the value that came from a size exclusion column was an absolute value." (Sept. Tr. 1292:21-1293:1 (Scandella); 1825:1-4 (Wall).)

Sandoz does not dispute that in 1987, Teva began experimenting with the use of copolymer-1 self-standards for SEC column calibration, correlating the results with molecular weights determined by viscosimetry. (DTX 3275 at TEV000304999-5000.) But the evidence presented at trial proves that this viscosimetry correlation method was not the first calibration method that Teva tried. Teva first tried globular proteins for column calibration. The same 1987 document cited by Teva to argue that globular proteins were not used to calibrate the SEC column, DTX 3275, describes calibrating the Superose 12 column with commercially available globular protein standards for molecular weight determination. (DTX 3275 at TEV000304991-92; Sept. Tr. 1230:13-1231:6 (Scandella).) Table 1 of that document shows the molecular weight results using globular protein standards, alongside the results from viscosity and ultracentrifugation measurements. (DTX 3275 at TEV000304998; Sept. Tr. 1232:1-19 (Scandella).) During his testimony in Teva's infringement case, Dr. Grant acknowledged that the scientists at Teva first calibrated the SEC column with globular proteins to measure the molecular weight of copolymer-1. (Sept. Tr. 278:23-279:1; 281:17-24.) Just a few days later, however, during his testimony in Teva's rebuttal to the defendants' invalidity case, he flip-flopped and denied that Teva ever did so. (Sept. Tr. 1453:20-1454:17; 1495:14-17; 1496:2-5; 1497:2-7.) Only when confronted on cross-examination with the Teva document that plainly states that the first standards used at Teva to calibrate the SEC column were commercially available protein standards, did Dr. Grant flip-flop again and admit that Teva did use globular proteins as standards for molecular weight determination. (Sept. Tr. 1498:1-18.) *See also* Sandoz's Response to ¶ 448, which is incorporated by reference.

Moreover, the documents introduced at trial demonstrate that the self-standard viscosimetry correlation method was not an effective method for molecular weight

determination, because Teva continued to experiment with alternative methods and calibration standards for at least 11 years, including measuring molecular weights by osmometry, MALLS, and MALDI-TOF mass spectrometry, and using polyethylene glycol, denatured protein, polylysine, histone, and synthesized peptide standards. (Sandoz's Opening FFCOL ¶¶ 88-116; DTX 3581 at 19.) Indeed, Teva's own consultant, W.R. Grace, told Teva in 1988 that "appropriate molecular weight standards have not yet been found," and that they had "already begun to work on the use of alternative molecular weight calibration standards for the size exclusion chromatography." (DTX 1762 at TEV000360353, TEV000360359; Sept. Tr. 1239:21-1240:21 (Scandella).)

Teva abandoned the viscosimetry correlation method in 1992 when it adopted self-standards whose molecular weights had been determined by MALLS. (DTX 1701; Sept. Tr. 1264:16-24 (Scandella).) According to Teva, the new calibration "assures a better determination" of molecular weight than the prior methods. (DTX 3510 at TEV001116323.) After continuing to experiment with the molecular weight measurement of copolymer-1, Teva abandoned the MALLS-based self-standards in 1998, when it adopted synthesized peptide standards. (DTX 3507.) That switch came after input from the FDA that copolymer-1 self-standards "may only serve for estimation of the relevant molecular weight values." (*Id.* at TEV000213922.) According to the Gad patents on the peptide standards, as of September 1998, "a need exists for molecular weight markers useful as standards for determining the molecular weight distribution of copolymer compositions contemplated by the invention." (DTX 3540 at col. 3:47-50.) In short, the overwhelming evidence makes clear that the viscosimetry correlation method was rejected by Teva and that even the replacement method using self-standards

characterized by MALLS was rejected by both Teva and the FDA. (*Id.*; DTX 3509 at TEV001116165; Sandoz's Opening FFCOL ¶¶ 112-114.)

478. Teva's 1987 method used size exclusion chromatography in which a Superose-12 column was calibrated using copolyqmer-1 whole polymer self-standards whose molecular weights had been determined by viscometry. (Sept. Tr. (Grant) 322:9-324:11, 1450:15-18, 1451:23-25, 1452:1-13; Sept. Tr. (Scandella) 1307:22-1308:2; Sept. Tr. (Wall) 1828:21-1829:5; DTX 3275 at TEV000304999-5000.)

Sandoz's Response:

As explained above, Teva's 1987 method also included the use of globular proteins. *See* Sandoz's Response to ¶ 477, which is incorporated by reference.

479. Teva had no difficulty in deciding to use size exclusion chromatography to determine the molecular weight of copolymer-1 or in deciding to use copolymer-1 self-standards to calibrate its columns. (DTX 4022 (Varkony Dep.) at 252:18-22, 252:24.) Significantly, no evidence was presented at trial that anyone working at Teva in 1987 on the measurement of the molecular weight of copolymer-1 had the credentials or experience of a person of ordinary skill in the art as defined by the experts in this case. (Sept. Tr. (Scandella) 1301:10-13; DTX 4016 (Gad 11/10/2009 Dep.) at 12:10-13.) In particular, there was no evidence that any Teva scientist in 1987 had any experience with SEC. Despite this, development of the calibration method only took Teva a matter of several weeks. (DTX 4022 (Varkony Dep.) at 110:2-9.)

Sandoz's Response:

Teva's suggestion that developing an acceptable calibration method for copolymer-1 took only several weeks is disingenuous and ignores the overwhelming evidence to the contrary that was presented at trial. As an initial matter, Teva omits the very next lines of Dr. Varkony's testimony:

> Q. Is it your testimony that it only took several weeks for Teva to figure out how to calibrate for determination of molecular weight of Copolymer-1?
>
> A. I have to check the records when we started and until we established the formal methodology. So I cannot say exactly if it is several weeks or more. I don't have the quantitative value.

(DTX 4022 at 110:10-18.) A review of the Teva "records" reveals the fallacy of Dr. Varkony's testimony and Teva's argument. Those records demonstrate that Teva engaged in extensive

experimentation for at least *eleven years*, i.e., 1987 to 1998, to find an acceptable SEC calibration standard and an acceptable method for measuring the molecular weights of its copolymer-1 self-standards. *See* Sandoz's Response to ¶ 477, which is incorporated by reference.

In 1987, the following scientists were persons of at least ordinary skill in the art under Dr. Scandella's and Dr. Grant's definition of that term: Dr. Michael Sela, Dr. Ruth Arnon, Dr. Irit Pinchasi, and Dr. Haim Varkony. *See* Sandoz's Opening FFCOL ¶ 73, which is incorporated by reference. None of the experts in this case testified that one of ordinary skill in the art must have had specific experience and skills in SEC in 1987. *See* Sandoz's Response to ¶ 444, which is incorporated by reference.

Teva's 1987-1998 documentation of its effort to characterize the molecular weight of copolymer-1 is probative of the complexities of copolymer-1 and the disparate molecular weight results one would have obtained in this timeframe, regardless of whether each individual Teva scientist and consultant was a person of ordinary skill in the art as defined in this case. *See Novo Nordisk*, 424 F.3d at 1362 ("[A]n inventor's failed attempts to practice an invention are relevant evidence of non-enablement."); *AK Steel*, 344 F.3d at 1244-45; *Enzo Biochem*, 188 F.3d at 1372-73. And in any case, Dr. Scandella confirmed that "Teva did what a person of average skill in the art would have done in 1994." (Sept. Tr. 1290:16-20 (Scandella).)

480. Teva recognized from the beginning that globular protein standards were inappropriate for determining the molecular weight of copolymer-1, because they resulted in molecular weights that were several times higher than the molecular weights obtained by other methods. (Sept. Tr. (Grant) 321:13-322:8, 1498:9-13, 1454:18-21, 1565:2-9, 1565:23-1566:9; DTX 3275 at TEV000304994-95; DTX 3510 at TEV001116321.)

<u>*Sandoz's Response:*</u>

The evidence in the record demonstrates that the first SEC calibration standards that Teva used were globular proteins. (DTX 3275 at TEV000304991-92; Sept. Tr. 1230:13-1231:6

(Scandella).) So it is incorrect that Teva "recognized from the beginning that globular protein standards were inappropriate." *See also* Sandoz's Response to ¶ 477, which is incorporated by reference. Moreover, Teva had the benefit of viscosity and ultracentrifugation data as a basis to make the conclusion that protein standards resulted in molecular weight that were several times higher than other methods. (DTX 3275 at TEV000304998.) No one other than Teva and its consultants had the benefit of those data. (Sept. Tr. 1232:20-1233:1 (Scandella).) And even after getting high molecular weight results with globular proteins, Teva's consultant suggested using globular proteins in a denatured state. (DTX 3538 at TEV000360386.)

481. Teva also recognized the reason for this inaccuracy: that proteins have a different hydrodynamic volume to molecular weight relationship than copolymer-1 molecules. (Sept. Tr. (Grant) 1565:2-9, 1565:23-1566:9; DTX 4022 (Varkony Dep.) at 63:20-64:5; DTX 3510 at TEV001116321.)

Sandoz's Response:

The term "inaccuracy" is not defined in this paragraph nor in the cited testimony and is not part of the Court's claim construction for the "molecular weight" limitations. To the extent Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is wrong. As Sandoz's experts testified, "SEC doesn't yield absolute molecular weights. It's not an absolute measurement method. So one wouldn't assume that the value that came from a size exclusion column was an absolute value." (Sept. Tr. 1292:21-1293:1 (Scandella); 1825:1-4 (Wall).) Moreover, even if one suspected that copolymer-1 had a different hydrodynamic volume or molecular shape from globular proteins, the proteins could still be appropriate SEC calibration standards, because one could have "simply reported the results as relative to globular protein standards," which is "widely done in size exclusion chromatography." (Sept. Tr. 1235:7-13 (Scandella).)

482. Teva used protein standards to test the performance and suitability of its size exclusion columns, but it did not use them to calibrate its columns for the purpose of determining

molecular weight. (Sept. Tr. (Grant) 1450:24-1451:22, 1453:20-1454:17; DTX 4022 (Varkony Dep.) at 62:24-63:2, 63:4-8, 63:10-16, 63:18-64:14, 64:17-21, 64:23-65:2; DTX 3510 at TEV001116321-22.)

Sandoz's Response:

The Teva documents introduced at trial are clear on their face that Teva used protein standards to calibrate its SEC columns for the molecular weight determination of copolymer-1. A 1987 Teva document, for example, describes calibrating the Superose 12 column with commercially available globular protein standards for molecular weight determination. (DTX 3275 at TEV000304991-92; Sept. Tr. 1230:13-1231:6 (Scandella).) Section 2.5 of that document is titled "Molecular Weight Calibration Standards" and subsection 2.5.1 is titled "Calibration kit for low molecular weight proteins":

2.5 Molecular Weight Calibration Standards

2.5.1 Calibration kit for low molecular weight proteins:

Pharmacia Cat. No. 17-0442-01 containing :

Albumin	Lot C623
Ovalbumin	Lot C626
Chymotry psinogen A	Lot C624
Ribonuclease A	Lot C625

(DTX 3275 at TEV000304991.) The document also states: "COP-1 is a highly charged linear polymer while the markers used in this study are globular proteins." (*Id.* at TEV000304995.) Table 1 of the document shows the molecular weight results using globular protein standards, alongside the results from viscosity and ultracentrifugation measurements. (*Id.* at TEV000304998; Sept. Tr. 1232:1-19 (Scandella).)

A 1988 W.R. Grace document is also clear on its face that Teva (and Grace) calibrated the SEC column with protein standards for molecular weight determination of copolymer-1. (DTX 3538 at TEV000360385.) In Table I of that document, the molecular weights of two copolymer-1 batches analyzed by various methods and SEC standards are shown. (*Id.*) One of

the columns shows the molecular weight results obtained by "(TEVA)" using "Size Exclusion" calibrated with "Proteins":

Table I
Molecular Weight

			Size Exclusion		
	Biological	Viscosity	PEG	Proteins	
COP I Batch	Activity	(TEVA)	(WRC)	(WRC)	(TEVA)
11A	25%	11,000	7400	62,000	47,000
13	85%	7,000	6500	56,000	42,000

(*Id.*)

Dr. Grant acknowledged that the scientists at Teva calibrated the SEC column with globular proteins to measure the molecular weight of copolymer-1:

> Q. So in 1987 when the scientists at Teva first decided to try to measure co-polymer-1, they used globular proteins to calibrate the SEC column?
>
> **1.** They used them for a short period of time.

(Sept. Tr. 281:17-24.) *See also* Sandoz's Responses to ¶ 448 and 477, which are incorporated by reference.

483. In fact, Teva's internal documents make clear that any references to proteins being used for molecular weight calibration instead of "system suitability" were in error. (Sept. Tr. (Scandella) 1308:23-1309:22; DTX 3510 at TEV001116322.)

Sandoz's Response:

Teva cites a single Teva document, DTX 3510, to support its statement about what "Teva's internal documents" purportedly show. Even that document, however, is clear on its face that proteins were used to calibrate the SEC column for molecular weight determination. In a section entitled "Selection of Markers for Column Calibration," Teva wrote:

> C) "Globular markers" (proteins) and copolymer-1 samples were injected under the same conditions into Superose 12 columns. The molecular weight of the copolymer-1 samples were calculated from the correlation between the elution volume (or retention time) and the log MW of protein markers.

(DTX 3510 at TEV00116321.) This passage confirms Teva's use of protein standards to calibrate the SEC columns for molecular weight. (Sept. Tr. 1277:15-1278:12 (Scandella).) *See also* Sandoz's Response to ¶ 482, which is incorporated by reference.

Contrary to Teva's representation to the Court, DTX 3510 does not state that "any references to proteins being used for molecular weight calibration instead of 'system suitability' were in error." Rather, after describing the use of protein standards as calibration markers for molecular weight, the document says: "to assure the correct function of the columns, a function test (erroneously called 'column calibration' instead of system suitability test of column performance) using protein markers was introduced." (DTX 3510 at TEV00116322.) On its face, this statement applies only to some unidentified prior document relating to a function test and containing the phrase "column calibration" with respect to protein markers. None of the evidence described above in Sandoz's Response to ¶ 482 fits that description, and that evidence is clear and unambiguous that Teva used globular proteins to calibrate the SEC columns for the molecular weight determination of copolymer-1. Thus, this "vague" statement does not stand for the sweeping proposition that Teva proposes, i.e., that Teva never used protein standards to calibrate the SEC columns for molecular weight. (Sept. Tr. 1309:21 (Scandella).) Had Teva never used protein markers for that purpose, it would have no basis for stating that "[t]he molecular weights of COP-1 batches calculated from the calibration curve of the [protein] markers (Fig. 1) were 4-5 times higher than those obtained by viscosity and ultracentrifuge

(Table 2)." (DTX 3275 at TEV000304994-95, TEV000304998; Sept. Tr. 1230:23-1231:6; 1231:16-25 (Scandella).)

484. In November 1992, Teva began using copolymer-1 self-standards whose molecular weights had been determined by a technique known as multi angle laser light scattering, or MALLS. The copolymer-1 self-standards were batches of copolymer-1 that had been made for the purpose of being calibration standards by adjusting the reaction time and temperature of the debenzylation step in the process of synthesizing copolymer-1. (DTX 1701; DTX 4022 (Varkony Dep.) at 58:4-16.)

Sandoz's Response:

Undisputed but incomplete. The MALLS molecular weights that Teva used for its self-standards were the Mn values even though they had data for Mw and Mz for the same samples. (DTX 1192 at TEV001162278, TEV001162280; Sept. Tr. 1263:5-11 (Scandella); 1493:12-1494:3 (Grant); DTX 4017 at 103:23-104:18 (Gad).) [redacted] The patents do not disclose that Mn values should be used for self-standards. (PTX 1.)

485. In June 1995, Teva submitted its original NDA to the FDA for approval. (Sept. Tr. (Grant) 1462:24-1463:4; Sept. Tr. (Wall) 1829:6-9.) Teva's Copaxone® NDA relied on copolymer-1 self standards for the molecular weight determination of Copaxone® batches, and the FDA ultimately approved Teva's NDA to market Copaxone® on that basis. (Sept. Tr. (Grant) 1462:24-1463:4.)

Sandoz's Response:

In 1995, prior to approving the NDA, the FDA requested that Teva switch from copolymer-1 self-standards to commercially available standards. (DTX 1770 at TEV000283327.) The FDA maintained its concerns over the validity of copolymer-1 self-standards as calibration markers after the NDA was approved:

> In the refuse to file letter questions were raised concerning the validity of these markers as primary calibration markers and concerning the validity of the values obtained from the calibration as determined, molecular weight values. It was stressed by FDA reviewers that the FDA cannot accept determinations based on

> markers for which the determinations were based on a method that in itself has a intrinsic margin of uncertainty.

(DTX 3507 at TEV000213922.) The FDA observed that copolymer-1 self-standards "may only serve for estimation of the relevant molecular weight values." (*Id.*) Teva itself had reached the same conclusion in 1995, observing that for SEC, "the sample molecular weight distribution and the calculated molecular weight averages are at best an approximation relative to the standard used. Copolymer-1 markers having the same structure and conformation have been prepared and are employed for estimation of molecular weights." (DTX 3509 at TEV001116165.) Teva even changed its molecular weight specifications because of this issue: "The term determination with respect to molecular weight was changed to estimation, *in response to FDA's expressed doubts about the accuracy furnished by a calibration based on glatiramer acetate markers*." (DTX 3507 at TEV000213922 (emphasis added).)

As Dr. Wall explained, the FDA "had considerable reservations about Teva using a proprietary marker and they made a recommendation that Teva actually either obtain a commercial marker or go to a laboratory that could do this in a way that could be reproduced by other individuals outside Teva." (Sept. Tr. 1829:13-18.) As Dr. Wall further explained, "FDA quite often approves things then asks you to do a follow-up long term study or change some calibration." (Sept. Tr. 1829:25-1830:2.) Moreover, one of skill in the art in 1994 would not have known the methods that Teva used in its NDA to measure the molecular weight of copolymer-1. (Sept. Tr. 1833:17-20 (Wall).)

486. None of the details of the development of Teva's particular molecular weight determination method were publicly available to persons of skill in the art in 1994.

<u>*Sandoz's Response:*</u>

Undisputed. Moreover, certain critical aspects of Teva's molecular weight determination method that cannot be called mere "details," such as which SEC calibration standards to use and

which independent analytical method to use for measuring the molecular weights of any self-standards, were also unavailable to the public in 1994. and none of this information was disclosed in any of the asserted patents. (Sept. Tr. 1227:21-1228:11; 1253:4-12; 1273:13-23 (Scandella); 1764:18-1765:25; 1826:4-14 (Wall).)

(2) Universal Calibration

487. In addition to self-standards, a person of skill in the art in 1994 could also have used universal calibration to accurately measure the peak molecular weight and molecular weight distribution (*e.g.*, the percentage of molecules between 2 and 20 kilodaltons or above 40 kilodaltons) of a sample of copolymer-1. (PTX 970 (Svec Dep.) at 320:2-7, 326:14-327:10, 320:22-321:10, 382:8-13, 384:23-385:6, 385:8-19; Sept. Tr. (Grant) 1430:8-1431:23.)

Sandoz's Response:

The term "accurately" is not defined in this paragraph nor in the cited testimony and is not part of the Court's claim construction for the "molecular weight" limitations. To the extent Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is wrong. As Sandoz's experts testified, "SEC doesn't yield absolute molecular weights. It's not an absolute measurement method. So one wouldn't assume that the value that came from a size exclusion column was an absolute value." (Sept. Tr. 1292:21-1293:1 (Scandella); 1825:1-4 (Wall).) In his deposition, Dr. Svec testified similarly:

> Q And you believe that's how a person skilled in your field would view any number given for a molecular weight value in a patent or a publication?
>
> A Under these conditions it is just a number that I can believe characterizes the specific polymer but I cannot tell anything about the accuracy of that number.

(PTX 970 at 331:23-332:6.)

Sandoz's experts also explained that universal calibration was not a common and widespread technique in the field of biotechnology and pharmaceutical products in 1994 or 1995

and that the use of universal calibration would not have enabled the claims. (Sept. Tr. 1284:13-18 (Scandella); Sandoz's Opening FFCOL ¶¶ 135-142.)

Moreover, the testimony from Dr. Svec that Teva cites does not support the proposition Teva advances. Dr. Svec testified that he has performed universal calibration on a material that was "part polyethylene glycol and part other monomers." (PTX 970 at 320:16-17.) He further testified that whether universal calibration gives accurate results "really depends case by case. For each polymer it is different." (*Id.* at 321:11-25; 322:12-20.) Neither Dr. Svec nor Teva contends that copolymer-1 is anything like a material that is "part polyethylene glycol and part other monomers." Dr. Svec's experience with universal calibration therefore sheds no light on the use of that technique for copolymer-1. Indeed, although Dr. Svec stated that the scientists working in his lab know how to carry out a universal calibration experiment, they are not experts in universal calibration. (*Id.* at 384:7-385:2.) To the extent Dr. Svec testified about obtaining a molecular weight for copolymer-1 using universal calibration, he did not state that one could have done so in 1994 or 1995. And he testified affirmatively that for universal calibration results for copolymer-1 to have any relevance to the asserted patents, one would need to know the precise standards and conditions used by Teva:

> Well, what you need to know and what is all this about is the fact that if you have all the conditions available, which means you know exactly all the conditions under which the separation has been achieved, you know what is the column, what is the hardware, software, everything, then using the same set of calibration standards you may get results that would be, as I said, very close to that that Teva is getting. If you go for different types of calibration and different types of standards no matter that you are using the universal calibration, the results may not be completely comparable.

(*Id.* at 378:18-379:5; *see also id.* at 386:4-20.) There is no mention of universal calibration in the asserted patents, and there is no evidence that Teva itself ever attempted to use it to measure the

molecular weight of copolymer-1. (Sept. Tr. 1286:13-15; (Scandella); 1534:25-1535:3 (Grant); PTX 1.)

Finally, Dr. Grant's testimony that universal calibration would have worked for copolymer-1 in 1994 is entitled to little, if any, weight. Dr. Grant is not an expert in universal calibration and has never even used universal calibration. (Sept. Tr. 268:25-269:8; 269:17-23 (Grant).)

488. According to the theory of universal calibration, the molecular weight values obtained from size exclusion chromatography should not be dependent on the type of standards used for calibration. (PTX 970 (Svec Dep.) at 356:2-8.) Unlike conventional size exclusion chromatography, universal calibration does not require the calibration standards to have the same hydrodynamic volume-to-molecular weight relationship as the sample, because it uses a different physical property (intrinsic viscosity) to allow a correlation of the size of molecules exiting the column to their molecular weight. (Sept. Tr. (Grant) 208:14-20, 1400:6-15.)

Sandoz's Response:

Application of universal calibration theory to copolymer-1 is problematic. Universal calibration is based on a fundamental assumption that separation in an SEC column, and thus the retention time, is based only on molecular size. (PTX 514 at 213; Sept. Tr. 1423:19-1424:22 (Grant).) Factors other than size, however, can influence the retention time, including "interaction between the column matrix and the sample, for example, ion exchange interactions." (Sept. Tr. 1200:1-4 (Scandella).) Universal calibration does not account for these interactions. (*See* PTX 514 at 216 ("The [universal calibration] method depends upon separation being size dominated and will break down if adsorption of polymer is significant").) Moreover, according to the authors of a 1989 article in the journal Analytical Biochemistry ("1989 Le Maire article"), "the concept of universal calibration requires several qualifications and can be used only as an approximation in most cases." (DTX 3353 at 51; Sept. Tr. 1287:14-1288:1.)

489. Universal calibration has been known since the late 1960s. By 1994, it was well described in the literature. There was extensive literature on universal calibration and a very large number of studies that showed that it worked quite well for a variety of different types of

polymers. (PTX 970 (Svec Dep.) at 296:16-22; Sept. Tr. (Grant) 1401:15-18, 1423:11-1430:7; PTX 514 at 213-17; PTX 553 at 73-76.) Furthermore, the ability to measure intrinsic viscosity was routine for persons of skill in the art in 1994. (PTX 970 (Svec Dep.) at 296:23-297:6.)

Sandoz's Response:

Universal calibration was not a common and widespread technique in the field of biotechnology and pharmaceutical products in 1994 or 1995. (Sept. Tr. 1284:13-18 (Scandella).) In addition, the universal calibration literature on which Dr. Grant relied at trial states that universal calibration equations apply to "any flexibly coiled molecule." (PTX 514 at 213; Sept. Tr. 1425:1-6 (Grant).) Dr. Grant testified that a flexibly coiled molecule is the same as a random coil. (Sept. Tr. 1425:7-23 (Grant).) Teva's measurements from 1993 demonstrate that copolymer-1 has secondary structure and is not a random coil. (DTX 1113 at TEV000312034.) In particular, Teva's results show that "[r]elatively high α-helical conformation (secondary structure) of COP-l was determined by circular dichroism and confirmed by FT-IR. A non-random distribution of helicity was found …. [I]n spite of a random synthesis, COP-l is, essentially, a mixture of polypeptides having a non-random primary structure of a certain α-helix secondary structure." (DTX 1113 at TEV000312034; Sept. Tr. 1202:11-1204:4 (Scandella).)

Even if copolymer-1 were random coil, universal calibration would still be problematic, because, as the authors of the 1989 Le Maire article conclude, "the inherent ambiguity in defining the molecular radius of macromolecules such as random coils and long rods, which in their conformation deviate very much from a compact, spherical shape, represents an obstacle to universal calibration of gel columns." (DTX 3353 at 55.) None of the literature cited by Teva teaches or suggests that universal calibration would work for a complex mixture of polypeptides such as copolymer-1.

490. A person skilled in the art in 1994 could have used the available scientific literature to set up and carry out universal calibration in order to determine the molecular weight

of copolymer-1 without significant experimentation. (Sept. Tr. (Grant) 1431:24-1432:11.)

Sandoz's Response:

See Sandoz's Responses to ¶¶ 487-489, which are incorporated by reference. In addition, Teva and its consultant W. R. Grace were aware of the possibility of using universal calibration for the molecular weight determination of copolymer-1 at least as early as May 1988. (DTX 3538 at TEV000360384; Sept. Tr. 1285:13-1286:12 (Scandella).) Despite being aware of universal calibration, there is no evidence in the record that Teva or any of its consultants ever used, or even tried using, universal calibration for the molecular weight determination of copolymer-1. (Sept. Tr. 1285:5-8 (Scandella); 1535:4-7 (Grant).)

491. Sandoz's expert Dr. Frantisek Svec, who was acknowledged by Sandoz's Dr. Scandella to be an expert in the use of universal calibration, agreed that universal calibration could be used to obtain accurate molecular weight results for a sample, and further that universal calibration could be used to obtain accurate molecular weights for copolymer-1:

> Q. So in your opinion a person of skill in the art could take a copolymer-1 sample and determine an accurate molecular weight?
>
> A. Yes. Take a sample and determine the molecular weight.

(PTX 970 (Svec 05/21/2010 Dep.) at 388:8-12; Sept. Tr. (Scandella) 1332:17-1334:13.)

Sandoz's Response:

Dr. Scandella did not testify that Dr. Svec was an expert in universal calibration:

> Q. Do you have any information that Dr. Svec is qualified as an expert in universal calibration or that he's used it?
>
> A. I don't know that he's an expert. I know he's used it.

(Sept. Tr. 1339:3-5.) In addition, to the extent Dr. Svec testified about obtaining a molecular weight for copolymer-1 using universal calibration, he did not state that one could have done so in 1994 or 1995. And he testified affirmatively that for universal calibration results for copolymer-1 to have any relevance to the asserted patents, one would need to know the precise

standards and conditions used by Teva. (PTX 970 at 378:18-379:5; *see also id.* at 386:4-20.) Dr. Svec testified that he could not evaluate whether or not the molecular weight values in the asserted patents were accurate because he did not know the standards and conditions. (*Id.* at 390:11-15.)

492. Dr. Scandella admitted that he has never performed universal calibration. (Sept. Tr. (Scandella) 1332:17-23.) Dr. Svec has experience and expertise actually performing universal calibration. (Sept. Tr. (Scandella) 1333:1-19.) Thus, the only evidence supports the conclusion that universal calibration can be used to accurately measure the molecular weight of copolymer-1.

Sandoz's Response:

The evidence does not support the conclusion that universal calibration can be used to accurately measure the molecular weight of copolymer-1. *See* Sandoz's Responses to ¶¶ 487-491, which are incorporated by reference.

493. Natco also believed that universal calibration could be used to measure the molecular weight of glatiramer acetate, and, indeed, Mylan has used universal calibration to report molecular weight values for copolymer-1 to the FDA. In particular, Mylan relied on an article from 1967, Z. Gallot-Brubisic et al., "Universal Calibration for Gel Permeation Chromatography, J. Polymer Science, Polymer Letters Edition (1967), to support the validity of the method. (PTX 963 (B. Rao 6/30/2010 Dep.) at 135:15-20, 136:19-137:3; Sept. Tr. (Owens) 601:24-603:1, 603:21-605:4; DTX 1411 at MYL0150490-91.) [redacted]

Sandoz's Response:

Teva neglects that the reason Mylan was able to use universal calibration to obtain molecular weight results for copolymer-1 is that it had the reference listed drug, Copaxone, in its possession and used the molecular weight of that material as a target for the universal calibration result. (DTX 1411 at MYL0150491; Sept. Tr. 604:6-17 (Owens).) Even with the reference listed drug, Mylan had to hire an outside consultant to develop the universal calibration method for copolymer-1, which took over a year of experimentation from 2009 to 2011. (Sept. Tr.

645:1-5 (Owens).) Mylan's experience in 2009 to 2011 sheds no light on the use of universal calibration for copolymer-1 in 1994, when the public would not have had access to the reference listed drug and would not have had a target material with which to work.

494. The trial record clearly shows that both self-calibration and universal calibration were available to persons of skill in the art of the patents in suit in 1994; that these techniques were well-described in the scientific literature; and that they could have been used to accurately determine the molecular weight of copolymer-1 samples.

Sandoz's Response:

See Sandoz's Responses to ¶¶ 447-493, which are incorporated by reference.

D. Conclusions of Law Concerning Definiteness

(i) The Molecular Weight Claim Terms Are Indefinite

495. A claim is not indefinite merely because the meaning of the claim is not plain on its face. *Exxon Research & Eng'g Co.*, 265 F.3d at 1375. "If the meaning of the claim is discernable, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, [the Federal Circuit has] held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Id.* Thus, only claims that are "insolubly ambiguous" even after the Court uses all tools at its disposal to try to construe the claims are invalid as indefinite. *See Source Search Techs., LLC*, 588 F.3d at 1076; *Star Scientific, Inc.*, 537 F.3d at 1371; *All Dental Prodx, LLC*, 309 F.3d at 780.

Sandoz's Response:

In August 2011, the Federal Circuit held that "a construed claim can be indefinite if the construction remains insolubly ambiguous, meaning it fails to provide sufficient clarity about the bounds of the claim to one skilled in the art." *Star Scientific*, 2011 U.S. App. LEXIS 17826 at *19. Thus, even if the claim can be construed, it may be still be held indefinite if the construction remains insolubly ambiguous. *Id.* The Federal Circuit has therefore made clear that the "not amenable to construction" test is not the only test for indefiniteness. *See also Source Search*, 588 F.3d at 1076 ("Only claims 'not amenable to construction' or 'insolubly ambiguous' are indefinite.").

496. As this Court has already found, the claims of the patents-in-suit are amenable to

construction. *Exxon Research & Eng'g Co.*, 265 F.3d at 1375; Claim Construction Order at 50-51. Throughout this case, the Court was presented with extensive evidence and has already rigorously analyzed whether the claim terms of the patents-in-suit are indefinite as a matter of law in the context of both claim construction and motions for summary judgment separately filed by both Defendants. No evidence was presented at trial that undermines the Court's claim construction decisions. To the contrary, the evidence presented at trial supports the Court's conclusion regarding the meaning of "average molecular weight" as used in the patent. (Sept. Tr. (Scandella) 1256:24-1257: 3; Sept. Tr. (Wall) 1828: 18-20; Sept. Tr. (Grant) 222:6-17; PTX 969 (Svec Dep.) at 9:19-23, 32:25-33:7, 34:18-22; PTX 962 (B. Rao 6/9/2010 Dep.) at 73:13-75:5, 116:3-13, 118:19-119:8; DTX 4022 (Varkony Dep.) 251:9-10, 251:12-18, 251:20-25, 252:3; PTX 964 (D. Rao Dep.) at 146:18-149:3, 174:17-178:13, 191:8-193:4; PTX 323 at MYL0001050-51, 58, 68-69, 73, 79-80, 84; PTX 281; PTX 741 at MYL0002927-932; PTX 349 at SDZ00017949; PTX 351 at SDZ00018608-11; PTX 986 at 26; PTX 317 at MYL0000110-11; PTX 959, 37:20-38:22; DTX 1701 at TEV001202496.)

Sandoz's Response:

See Sandoz's Response to ¶ 495, which is incorporated by reference. Sandoz does not dispute that the Court construed "average molecular weight" to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column," but that construction remains indefinite. *Star Scientific*, 2011 U.S. App. LEXIS 17826 at *19. Because there were multiple ways to appropriately calibrate an SEC column in 1994, and the resulting molecular weights would not have been the same, the term "appropriately calibrated suitable gel filtration column" is insolubly ambiguous. (Sept. Tr. 1293:3-7 (Scandella); 1824:3-25 (Wall).) The Court's analysis of the "standards and conditions" issue in the August 24, 2011 Claim Construction Order pre-dates both the *Star Scientific* case and the evidence presented at trial on this issue. Documents and testimony from the trial make clear that "average molecular weight," as construed "fails to provide sufficient clarity about the bounds of the claim to one skilled in the art." *Star Scientific*, 2011 U.S. App. LEXIS 17826, at *19. *See* Sandoz's Opening FFCOL ¶¶ 54-148, 164-167.

(ii) Sandoz's "No Standards" Indefiniteness Argument

497. According to Sandoz, without knowing the precise calibration standards used by Teva, and the manner in which the molecular weights of the standards was determined, a person

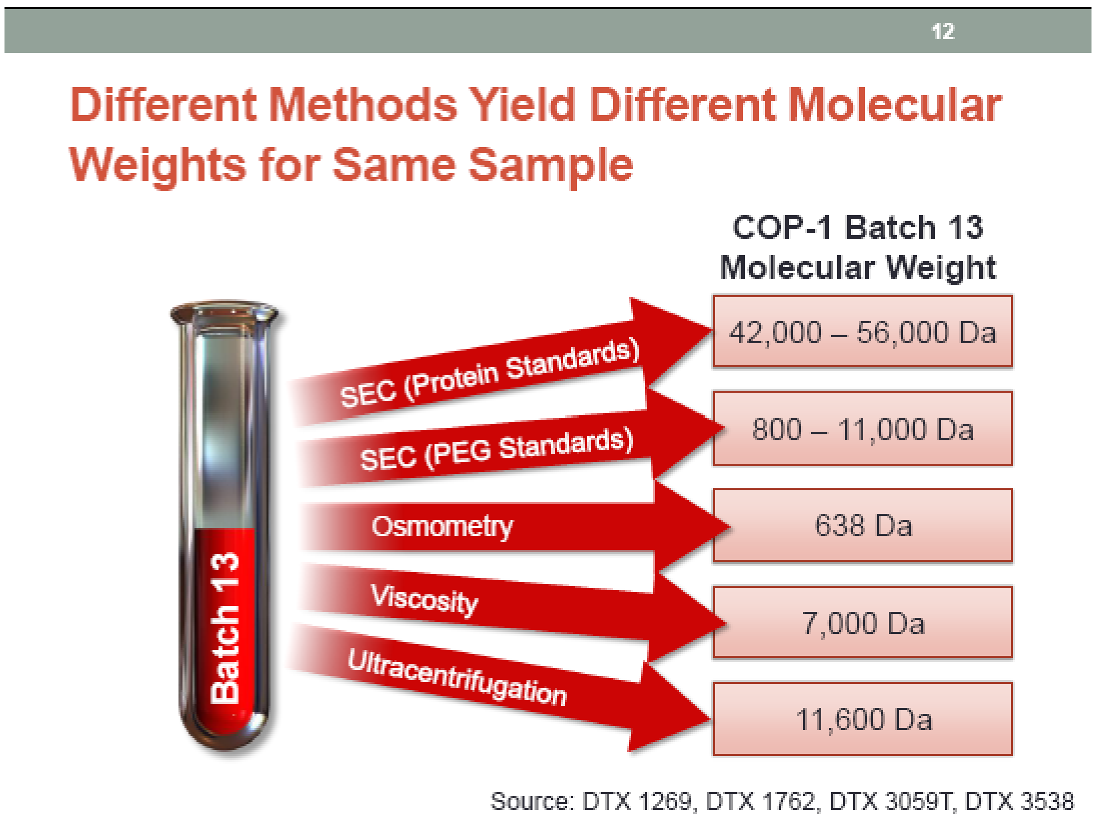
of skill in the art would have been unable to determine whether a copolymer-1 sample meets the claim limitations. This argument fails for at least the following reasons: First, there is no dispute that the level of skill in the art is high, and there is no evidence that such a highly skilled person would have been unable to accurately determine the molecular weight of a copolymer-1 sample. Second, the evidence at trial demonstrated that prior to the filing date of the patents-in-suit persons of skill would have understood from the scientific literature how to accurately determine the molecular weight of polydisperse polypeptide mixtures like copolymer-1. Dr. Grant testified regarding prior art texts and publications that explain how the molecular weight of polymers like copolymer-1 could be measured as of 1994. None of that prior art evidence was challenged. Third, Sandoz's reliance on the work done by Teva does not undermine this conclusion. As a matter of law, Teva's internal work is irrelevant to the analysis of whether the claims of the patent are definite. Moreover, even if relevant, Teva's experience shows that more than one type of standard (or method of measuring the molecular weights of standards) can be used to obtain accurate molecular weights for copolymer-1. (Sept. Tr. (Grant) 1452:1-13; DTX 3275; DTX 1701.) In fact, no evidence was presented at trial demonstrating that a person of skill was unable to accurately determine the "average molecular weight" of a copolymer-1 sample as that term has been interpreted by the Court based upon the disclosure of the patents-in-suit.

Sandoz's Response:

First, Sandoz's experts did not testify that the level of skill was "high." Second, the term "accurately" is not defined in this paragraph, and to the extent Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is wrong. (Sept. Tr. 1292:21-1293:1 (Scandella); 1825:1-4 (Wall).) Teva's arguments about determining an "accurate" molecular weight therefore have no relevance to SEC or to the issue of indefiniteness.

Third, Teva is mistaken that its internal work "shows that more than one type of standard (or method of measuring the molecular weights of standards) can be used to obtain accurate molecular weights for copolymer-1." Neither of the documents it cites remotely support that proposition. DTX 3275 contains a table showing the molecular weight results for copolymer-1 using three different methods, with highly variable results that differ by thousands of daltons across methods. (DTX 3275 at TEV000304998; Sept. Tr. 1232:1-19 (Scandella).) DTX 1701 is a Teva protocol for measuring the molecular weight of copolymer-1; it does not contain any comparison of molecular weight from different methods that would support Teva's statement. There was overwhelming evidence presented at trial that measuring the molecular weight of

copolymer-1 is difficult, uncertain, and yields results that are highly discrepant, depending on the analytical methods and SEC standards that are used. *See* Sandoz's Opening FFCOL ¶¶ 77-78, 85-114, 123-132. The molecular weight results for Teva's copolymer-1 batch 13 exemplify the problem:



(DTX 3581 at 12; Sept. Tr. 1259:13-1260:15 (Scandella).)

Despite document after document showing the highly discrepant results that Teva's Ph.D. scientists and Teva's highly experienced consultants obtained when attempting to measure the molecular weight of copolymer-1 using different methods and different SEC standards, *see* Sandoz's Opening FFCOL ¶¶ 77-78, 85-114, 123-132, Teva now tells the Court that "*no evidence* was presented at trial demonstrating that a person of skill was unable to accurately determine" the average molecular weight of copolymer-1. That attorney argument is flatly contradicted by the documents and testimony cited above, including the 1995 document where

Teva's consultant Dr. Krull stated: "At issue here is the observation that COP-1 results in terms of MW and MW distributions appear to vary from method to method and sample to sample," and that unless certain problems were addressed and overcome, "we can never have comparable results." (DTX 1744 at TEV001017877-78; Sept. Tr. 1512:13-1513:3 (Grant).)

Fourth, Teva introduced no literature at trial and cites no literature here that describes how to overcome the difficulties associated with molecular weight analysis of a material as complex as copolymer-1. Teva is incorrect that the prior art publications cited by Dr. Grant were unchallenged at trial. Dr. Wall specifically rebutted Dr. Grant's testimony that these publications were useful for the molecular weight determination of copolymer-1:

> Q. Now, Dr. Grant testified that the several SEC textbooks taught how to use self standards to determine the molecular weight of copolymer-1. Do you agree with that, that the textbooks available at the time in 1994 or 1995 would have taught one of skill in the art how to use SEC to measure the molecular weight of copolymer-1?
>
> A. Oh, absolutely not. They may have taught you to use self standards to determine the molecular weight of much simpler polypeptides or polymers, but nothing as complicated as copolymer-1.
>
> Q. And why is it that you couldn't apply the teachings of textbooks to the more complicated copolymer-1 mixture?
>
> A. Well, as I said, there are a whole range of uncertainties about the molecular size, its shape its conformation, so all of those things would confound the use of self standards and even when the person of ordinary skill had determined, made self standards, determined their molecular weight by 1 out of 5 or 6 or whatever absolute molecular weight determination, you still wouldn't know if those were the kind of standards used by Teva in arriving at the 5 to 9 kd ranges listed in the patent.

(Sept. Tr. 1820:25-1821:19.)

Finally, Teva misrepresents the law by arguing that its internal work is irrelevant "as a matter of law." Teva cites no authority for this proposition. To the extent Teva is relying on the *Johns Hopkins* case from ¶ 442, that reliance is misplaced. *Johns Hopkins* did not hold that all

persons working in a patentee's laboratory must have been persons of ordinary skill in the art for the laboratory work to be relevant to the undue experimentation inquiry. Moreover, the court did not hold that the data obtained by scientists in patentee's laboratory should be disregarded. Nor did the court hold that expert testimony concerning what one of ordinary skill in the art would have done at a certain point in time could not be informed by what those in the patentee's laboratory actually did. In addition, the *Johns Hopkins* court rejected the defendant's reliance on the work in patentee's laboratory because defendant "produced *no evidence* concerning the level of skill of those individuals" working in the lab. *Johns Hopkins*, 152 F.3d at 1360 (emphasis added). Here, by contrast, Sandoz has produced ample evidence to demonstrate that Teva scientists and consultants were persons of ordinary skill in the art. (Sandoz's Opening FFCOL ¶¶ 73-76.) *See also Novo Nordisk*, 424 F.3d at 1362 ("[A]n inventor's failed attempts to practice an invention are relevant evidence of non-enablement."); *AK Steel*, 344 F.3d at 1244-45; *Enzo Biochem*, 188 F.3d at 1372-73.

(1) <u>Self-Standards Could Not Have Been Used to Determine a Single Molecular Weight of Copolymer-1</u>

498. A person of ordinary skill in the art with the knowledge and experience described above could determine whether a copolymer-1 sample falls within the scope of the molecular weight limitations of the asserted claims using the information disclosed in the patents. It is undisputed that the specification specifically tells a person of ordinary skill to use size exclusion chromatography to determine the molecular weight of copolymer-1. (*See* PTX 1, at col. 3:6-8 (noting that molecular weight "was determined on a calibrated gel filtration column (Superose 12)".)

<u>*Sandoz's Response:*</u>

See Sandoz's Response to ¶ 445, which is incorporated by reference.

499. Defendants have not established by clear and convincing evidence that a person of ordinary skill in the art could not discern the boundaries of the claims as construed by the Court. *Power-One, Inc.*, 599 F.3d at 1350.

Sandoz's Response:

Sandoz has met its burden with ample documentary and testimonial evidence regarding the inability of one of ordinary skill in the art to understand the scope of the molecular weight claims without knowing the calibration standards used by the patentees. (*See* Sandoz's Opening FFCOL ¶¶ 54-148, 164-167.)

(a) Self-Standards for Copolymer-1 Had Not Been Described in the SEC Literature by 1994

500. The evidence presented at trial demonstrated that size exclusion chromatography was a well-understood and well-described technique at the time the patent application was filed in 1994. (Sept. Tr. (Grant) 1421:4-24, 1400:16-21, 1401:9-11, 1414:8-1415:17, 1418:7-1421:3; PTX 514; PTX 566.) While calibration of the column was required, a person of ordinary skill could have used self-standards (either whole polymer or fractionated standards) to calibrate the SEC column. (Sept. Tr. (Grant) 1399:18-1400:13.) And while there were multiple "absolute" methods to measure the molecular weight of the self-standards, a person of ordinary skill would have known how to analyze that data to obtain a calibration curve that would result in an accurate molecular weight measurement by size exclusion chromatography. (Sept. Tr. (Grant) 327:9-16, 1403:3-13, 1421:4-24.) There is no need to describe such methods in the patent itself because, as shown through Dr. Grant's testimony, these techniques were well-known to the person of ordinary skill the art in 1994. (Sept. Tr. (Grant) 1421:4-24.) The law is clear—a patent applicant is not required to describe information in the patent specification that would be well-known to the person of skill in the art. *Koito Mfg. Co., Ltd.*, 381 F. 3d at 1156.

Sandoz's Response:

The term "accurate" is not defined in this paragraph, and to the extent Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is wrong. (Sept. Tr. 1292:21-1293:1 (Scandella); 1825:1-4 (Wall).) Teva's arguments about determining an "accurate" molecular weight therefore have no relevance to SEC or to the issue of indefiniteness.

Teva introduced no literature at trial and cites no literature here that describes how to create self-standards for a material as complex as copolymer-1. (*See* Sept. Tr. 1820:25-1821:19.) Moreover, Dr. Scandella and Dr. Wall testified at length about the problems with using copolymer-1 self-standards for SEC calibration. (Sandoz's Opening FFCOL ¶¶ 122-133.) In particular, even if one made a copolymer-1 self-standard, "there was no good way to measure the

molecular weight of a cop-1 standard in 1994." (Sept. Tr. 1251:25-1252:1 (Scandella).) That is because different molecular weight methods yield very different results for a given copolymer-1 sample or standard, as shown by an abundance of documents at trial. (Sandoz's Opening FFCOL ¶¶ 77-132.) *See also* Sandoz's Responses to ¶¶ 447-476 and 497, which are incorporated by reference.

The one-sentence molecular weight description in the patents does not provide one of ordinary skill in the art with enough information to obtain a proper calibration curve using copolymer-1 self-standards. Dr. Scandella testified that if copolymer-1 self-standards were the intended calibration method of the asserted patents, additional information should have been included in the patents about the self-standards. (Sept. Tr. 1253:1-13 (Scandella).) That information includes "detailed conditions of how they were synthesized and purified…how they were characterized and what method and what type of molecular weight average and so forth was used," all of which is "information that one would need in order to reproduce this material." (Sept. Tr. 1253:4-12 (Scandella).) As the Federal Circuit has explained, a patentee "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *ALZA*, 603 F.3d at 941.

501. Because a person of ordinary skill could discern whether a copolymer-1 sample fell within the numerical molecular weight limitations of the asserted claims by using self-standards, the claims are not indefinite. *See Power-One, Inc.*, 599 F.3d at 1350; *Exxon Research & Eng'g Co.*, 265 F.3d at 1379.

Sandoz's Response:

Because there were multiple ways to appropriately calibrate an SEC column in 1994, and the resulting molecular weights would not have been the same, the term "appropriately calibrated suitable gel filtration column" is insolubly ambiguous. (Sept. Tr. 1293:3-7 (Scandella); 1824:3-25 (Wall).) *See* Sandoz's Response to ¶ 500, which is incorporated by reference.

(b) Teva Developed Self-Standards With Significant Difficulty and Ultimately Abandoned Them

502. Defendants spent a significant amount of time at trial offering evidence regarding a relatively few Teva internal research documents and documents generated by Teva's outside contractors. What Teva itself did, however, is irrelevant to the question of indefiniteness. *See* No. 08-cv-7611, D.I. 181, Memorandum and Order, September 7, 2010, at 3-4 (denying motion to strike expert declarations and noting that experts did not need information on what Teva actually did to render opinions on indefiniteness). A patent must provide a sufficient disclosure to allow a person of ordinary skill in the art to discern the metes and bounds of the claims, and determine whether an accused product falls within their scope, but there is no requirement that it provide a disclosure that allows replication of the patentee's underlying research. *Exxon Research & Eng'g Co.*, 265 F.3d at 1375; *Kinetic Concepts, Inc.*, 554 F.3d at 1022.

Sandoz's Response:

Teva's 1987-1998 documentation of its effort to characterize the molecular weight of copolymer-1 is probative of the complexities of copolymer-1 and the disparate molecular weight results one would have obtained in this timeframe, depending on the calibration chosen. *See Novo Nordisk*, 424 F.3d at 1362; *AK Steel*, 344 F.3d at 1244-45; *Enzo Biochem*, 188 F.3d at 1372-73. That effort is therefore probative of whether the mere disclosure of a "calibrated gel filtration column" in the patent is sufficient to render the claims definite.

Sandoz does not contend that the patents must allow "replication of the patentee's underlying research," but agrees that the patents must "provide a sufficient disclosure to allow a person of ordinary skill in the art to discern the metes and bounds of the claims," and have "the same" composition. 35 U.S.C. 112 ¶ 1 requires that the patents enable persons of skill in the art to make the same composition as claimed. The patents fail to do so. The one-sentence molecular weight description in the patents does not provide one of ordinary skill in the art with enough information to obtain a proper calibration curve using copolymer-1 self-standards and thereby assess the scope of the claims. (*See* Sept. Tr. 1253:1-13; 1253:4-12 (Scandella).)

503. If what Teva did during its development were relevant to the question of definiteness, the evidence reinforces the conclusions that (1) self-standards could be used to measure the molecular weight of copolymer-1; and (2) the molecular weights of those self-

standards could be measured using more than one absolute technique. The evidence shows that in its very first method for measuring the molecular weight of copolymer-1, Teva used self-standards to calibrate its SEC columns and determine the molecular weight of copolymer-1. (Sept. Tr. (Grant) 321:6- 324:11, 1450:15-18, 1451:23-25, 1452:1-3, 1462:18-23; Sept. Tr. (Scandella) 1307:22-1308:2; Sept. Tr. (Wall) 1828: 21-1829:5; DTX 3275.) By August 1987—over three months before Teva and Weizmann entered into a formal collaboration agreement on the development of copolymer-1—Teva had already developed a method for determining molecular weight of copolymer-1 using self-standards whose molecular weights had been determined by viscometry. (Sept. Tr. (Grant) 1452:4-13; DTX 1232; DTX 3275 at TEV000304999-5000.) Haim Varkony, Teva's head of Chemistry, Manufacturing, and Controls (CMC) and Biological Development in Innovative R&D, testified that Teva developed its column calibration method in a matter of a few weeks. (DTX 4022 (Varkony Dep.) at 110:2-9.) He also testified that Teva had no difficulty in deciding to use SEC or in deciding to use copolymer-1 self-standards for calibration. (DTX 4022 (Varkony Dep.) at 252:18-22, 252:24.) Subsequently, Teva used the absolute measurement technique of multi-angle laser light scattering to measure the molecular weights of its self-standards. (DTX 1701; DTX 4022 (Varkony Dep.) at 58:4-6.)

Sandoz's Response:

The "very first method" that Teva used to measure the molecular weight of copolymer-1 did not involve self-standards; rather, Teva used globular protein standards. *See* Responses to ¶ 477 and 482, which are incorporated by reference.

Moreover, Dr. Scandella and Dr. Wall testified at length about the problems with using copolymer-1 self-standards for SEC calibration. (Sandoz's Opening FFCOL ¶¶ 122-133.) In particular, even if one made a copolymer-1 self-standard, "there was no good way to measure the molecular weight of a cop-1 standard in 1994." (Sept. Tr. 1251:25-1252:1 (Scandella).) That is because different molecular weight methods yield very different results for a given copolymer-1 sample or standard, as shown by an abundance of documents at trial. (Sandoz's Opening FFCOL ¶¶ 77-132.) *See also* Sandoz's Responses to ¶¶ 447-476 and 497, which are incorporated by reference.

Sandoz does not dispute that in 1987, Teva began experimenting with the use of copolymer-1 self-standards for SEC column calibration, correlating the results with molecular weights determined by viscosimetry. (DTX 3275 at TEV000304999-5000.) But the documents

introduced at trial demonstrate that the self-standard viscosimetry correlation method was not an effective method for molecular weight determination, because Teva continued to experiment with alternative methods and calibration standards for at least 11 years, including osmometry, MALLS, and MALDI-TOF mass spectrometry methods, and polyethylene glycol, denatured protein, polylysine, histone, and synthesized peptide standards. (Sandoz's Opening FFCOL ¶¶ 88-116; DTX 3581 at 19.) Indeed, Teva's own consultant, W.R. Grace, told Teva in 1988 that "appropriate molecular weight standards have not yet been found," and that they had "already begun to work on the use of alternative molecular weight calibration standards for the size exclusion chromatography." (DTX 1762 at TEV000360353, TEV000360359; Sept. Tr. 1239:21-1240:21 (Scandella).)

Teva abandoned the viscosimetry correlation method in 1992 when it adopted self-standards whose molecular weights had been determined by MALLS. (DTX 1701; Sept. Tr. 1264:16-24 (Scandella).) Teva chose the Mn values from the MALLS molecular weight data for its self-standards solely because the Mn values "would make the best match for the existing fixed calibration curve that was used before." (DTX 1192 at TEV001162278, TEV001162280; Sept. Tr. 1263:5-11 (Scandella); 1493:12-1494:3 (Grant); DTX 4017 at 103:23-104:25 (Gad).) After continuing to experiment with the molecular weight measurement of copolymer-1, Teva abandoned the MALLS-based self-standards in 1998, when it adopted synthesized peptide standards. (DTX 3507.) That switch came after input from the FDA that copolymer-1 self-standards "may only serve for estimation of the relevant molecular weight values." (*Id.* at TEV000213922.) According to the Gad patents on the peptide standards, as of September 1998, "a need exists for molecular weight markers useful as standards for determining the molecular weight distribution of copolymer compositions contemplated by the invention." (DTX 3540 at

col. 3:47-50.) In short, the overwhelming evidence makes clear that the viscosimetry correlation method was rejected by Teva and that even the replacement method using self-standards characterized by MALLS was rejected by both Teva and the FDA. (*Id.*; DTX 3509 at TEV001116165; Sandoz's Opening FFCOL ¶¶ 112-114.)

Teva's suggestion that developing an acceptable calibration method for copolymer-1 took only several weeks ignores the overwhelming evidence to the contrary that was presented at trial. Teva omits the very next lines of Dr. Varkony's testimony:

> Q. Is it your testimony that it only took several weeks for Teva to figure out how to calibrate for determination of molecular weight of Copolymer-1?
>
> A. I have to check the records when we started and until we established the formal methodology. So I cannot say exactly if it is several weeks or more. I don't have the quantitative value.

(DTX 4022 at 110:10-18.) A review of the Teva "records" reveals the fallacy of Dr. Varkony's testimony and Teva's argument. As explained above, those records demonstrate that Teva engaged in extensive experimentation for at least *eleven years*, i.e., 1987 to 1998, to find an acceptable SEC calibration standard and an acceptable method for measuring the molecular weights of its copolymer-1 self-standards.

(2) <u>Universal Calibration Was Known in 1994 But Would Not Have Worked for Copolymer-1</u>

504. In addition to self-standards, the record at trial also demonstrated that universal calibration was available to a person of skill in the art in 1994 and that such persons could have used that technique to accurately determine the molecular weight of copolymer-1. Using this method, a person of ordinary skill could discern the scope of the claims and whether a particular copolymer-1 batch met the limitations of those claims, and hence the claims are not indefinite. *See Power-One, Inc.*, 599 F.3d at 1350; *Exxon Research & Eng'g Co.*, 265 F.3d at 1379.

<u>Sandoz's Response:</u>

The term "accurately" is not defined in this paragraph nor in the cited testimony and is not part of the Court's claim construction for the "molecular weight" limitations. To the extent

Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is wrong. (Sept. Tr. 1292:21-1293:1 (Scandella); 1825:1-4 (Wall); *see also* PTX 970 at 331:23-332:6 (Svec).) Dr. Scandella explained that universal calibration was not a common and widespread technique in the field of biotechnology and pharmaceutical products in 1994 or 1995. (Sept. Tr. 1284:13-18 (Scandella).) There is no mention of universal calibration in the asserted patents. (Sept. Tr. 1286:13-15; (Scandella); 1534:25-1535:3 (Grant); PTX 1.) Dr. Svec explained that for universal calibration results for copolymer-1 to have any relevance to the asserted patents, one would need to know the precise standards and conditions used by Teva:

> Well, what you need to know and what is all this about is the fact that if you have all the conditions available, which means you know exactly all the conditions under which the separation has been achieved, you know what is the column, what is the hardware, software, everything, then using the same set of calibration standards you may get results that would be, as I said, very close to that that Teva is getting. If you go for different types of calibration and different types of standards no matter that you are using the universal calibration, the results may not be completely comparable.

(PTX 970 at 378:18-379:5; *see also id.* at 386:4-20.) *See also* Sandoz's Responses to ¶¶ 488-490, which are incorporated by reference.

505. Universal calibration was first described in the late 1960s, and by 1994, there was extensive literature on universal calibration and a large number of studies that showed that this technique worked quite well for different types of polymers. (PTX 970 (Svec Dep.) at 296:16-22, Sept. Tr. (Grant) 1401:12-18; PTX 514 at 213-17; PTX 553 at 73-76.) Dr. Grant testified that in 1994, a person of skill in the art could have used universal calibration to accurately determine the peak average molecular weight and the molecular weight distribution of a copolymer-1 sample or a sample of TFA copolymer-1 without undue experimentation. (Sept. Tr. (Grant) 1430:8-1432:11; PTX 970 at 382:8-382:13; 384:23-385:6: 385:8-385:19.) It is unrebutted that universal calibration was known to persons skilled in the art in 1994, and that it could readily be used to accurately determine the average molecular weight and the molecular weight distribution of a sample of copolymer-1.

Sandoz's Response:

See Sandoz's Responses to ¶¶ 488-490, which are incorporated by reference. In addition, Dr. Grant's testimony that universal calibration would have worked for copolymer-1 in 1994 is

entitled to little, if any, weight. Dr. Grant is not an expert in universal calibration and has never even used universal calibration. (Sept. Tr. 268:25-269:8; 269:17-23 (Grant).)

506. In sum, Defendants have failed to carry their burden of proving by clear and convincing evidence that the claims are indefinite. The Court has already construed "average molecular weight," and the evidence adduced at trial shows that persons of skill in the art in 1994 would have understood how to accurately measure the "average molecular weight" of copolymer-1 using either self-standards or universal calibration, both of which were well-known methods. A person of ordinary skill in the art, based upon the disclosures in the patent and her own knowledge, could thus discern the scope of the claims. The claims of the patents-in-suit are definite. *See Power-One. Inc.*, 599 F.3d at 1350; *Exxon Research & Eng'g Co.*, 265 F.3d at 1379.

Sandoz's Response:

Sandoz has met its burden with ample documentary and testimonial evidence regarding the inability of one of ordinary skill in the art to understand the scope of the molecular weight claims or reproduce the claimed invention without knowing the calibration standards. (*See* Sandoz's Opening FFCOL ¶¶ 54-148, 164-167.)

E. Conclusions of Law Concerning Enablement

507. Out of the same set of assertions used to support its indefiniteness theory, Sandoz fashions an argument that the asserted claims likewise do not satisfy the enablement requirement of 35 U.S.C. § 112. Section 112 requires a patent specification to provide a description of the invention "as to enable any person skilled in the art to which it pertains . . . to make and use [the invention]." 35 U.S.C. § 112.

Sandoz's Response:

Although Sandoz's lack of enablement defense and indefiniteness defense have some overlapping factual bases, they are not based on the "same set of assertions." *See* Sandoz's Opening FFCOL ¶¶ 54-148 (lack of enablement) and ¶¶ 163-167 (indefiniteness). In addition, Teva's quotation of Section 112 omits important language, including the key phrase "the same." Section 112 requires that a patent specification include "a written description of the invention, and of the manner and process of making and using it, in such *full, clear, concise, and exact*

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use *the same*." 35 U.S.C. § 112, ¶ 1 (emphasis added).

508. As discussed above in ¶¶ 438-443, in determining whether a claim is enabled, courts have looked the seven *Wands* factors set forth in *In re Wands*, 858 F.3d at 737.

Sandoz's Response:

There are eight *Wands* factors. *In re Wands*, 858 F.3d at 737.

509. Here, Defendants have failed to carry their burden of proving by clear and convincing evidence that the asserted claims are invalid for lack of enablement. There was no evidence presented at trial demonstrating that a person of skill in the art would have been unable to make and use a lower molecular weight copolymer-1 as claimed in the patents-in-suit. To the contrary, the evidence presented at trial demonstrated that the highly skilled person of skill in the art of the patents-in-suit had at their disposal the information necessary to make the claimed lower molecular weight copolymer-1 and measure its molecular weight to determine whether it met the claim limitations without undue experimentation.

Sandoz's Response:

Sandoz has met its burden of proving with clear and convincing evidence the inability of one of ordinary skill in the art to reproduce the claimed invention without knowing the calibration standards and other aspects of the calibration procedure used by the patentees. (*See* Sandoz's Opening FFCOL ¶¶ 54-148.) Rather than confront this evidence directly, Teva makes the remarkable declaration that "no evidence" was presented at trial about the difficulty one of skill in the art would have making copolymer-1 with the claimed molecular weight. At trial, Sandoz presented document after document showing the highly discrepant results that Teva's Ph.D. scientists and Teva's highly experienced consultants got when attempting to measure the molecular weight of copolymer-1 using different methods and different SEC standards, and Sandoz presented extensive testimony from Dr. Scandella and Dr. Wall regarding the undue experimentation required to reproduce the claimed invention. (*See, e.g.*, Sept. Tr. 1227:21-1228:11; 1273:13-1274:3 (Scandella); 1764:18-1765:25; 1825:11-19 (Wall); Sandoz's Opening FFCOL ¶¶ 72-78, 85-114, 123-132.)

(i) The Level of Skill In the Art

510. Looking first at *Wands* factor 6, the parties and the experts unanimously agree that the level of skill in the art of the patents-in-suit is high. (*See* Sept. Tr. (Grant) 189:22-190:6; Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9; Sept. Tr. (Zeiger) 809:10-811:15; PTX 806 at 3; PTX 4030 at 4.) Defendants face the burden, therefore, of proving by clear and convincing evidence that such a highly-skilled scientist would not have been able to make and use the claimed lower molecular weight copolymer-1. *In re Wands*, 858 F.2d at 740 (weighing the high level of skill in the art in holding that undue experimentation would not be required).

Sandoz's Response:

Sandoz's experts did not testify that the level of skill was "high." Moreover, no level of skill would remedy Teva's inadequate disclosure of molecular weight methodology, because the patents do not even teach the starting point, *i.e.*, the SEC calibration standards. (Sept. Tr. 1227:21-1228:11 (Scandella); 1764:18-1765:25 (Wall).) Persons skilled in the art are left to choose from a variety of commercial standards, or develop their own set of standards and choose one of many methods to obtain the necessary, independent molecular weight values for those self-standards. (DTX 3581 at 19; Sept. Tr. 1293:15-1295:1 (Scandella).) At the end of that process, the molecular weight results for the copolymer-1 self-standards would vary widely, depending on the method chosen, confounding any attempt to reproduce the claimed invention. (*E.g.*, DTX 3137 at TEV000290819.) *See also* Sandoz's Opening FFCOL ¶¶ 156-157.

(ii) The Prior Art and the Patent Provide Inadequate Guidance to Measuring Molecular Weight of Copolymer-1 Using Size Exclusion Chromatography

511. Turning next to *Wands* factors 2, 5, and 7, the trial evidence also showed that the highly skilled person of skill in the art would have had access to a large body of scientific literature, published over the course of many years, describing how to carry out SEC on polydisperse polymers like copolymer-1. The patents specifically direct a person of skill to use size exclusion chromatography, and the prior art gave significant direction and guidance to the person of skill in the art on that technique. (PTX 566; Sept. Tr. (Grant) 1410:10-1412:5, 1414:8-21, 1418:19-1419:21; PTX 553 at 70.) As discussed above, a person of ordinary skill could have calibrated an SEC column, to obtain an accurate molecular weight for copolymer-1, using either self-standards or universal calibration. Moreover, there was no evidence presented at trial that the science involved in the molecular weight determination of copolymer-1 is poorly understood or unpredictable or that the determination of the molecular weight of copolymer-1 using SEC would have presented any significant problems for the person of skill in the art.

Sandoz's Response:

The patents provide only one sentence on how to determine the molecular weight of copolymer-1: "The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12)." (PTX 1, col. 3:6-8.) There is no other direction or guidance on how to calibrate the SEC column to make the same copolymer-1 that is claimed. As the Federal Circuit held in *Enzo v. Calgene*, "the teachings set forth in the specifications provide no more than a 'plan' or 'invitation' for those of skill in the art to experiment...they do not provide sufficient guidance or specificity as to how to execute that plan." *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999). The one-sentence molecular weight disclosure is particularly egregious given that Teva had possession of detailed molecular weight calibration procedures, including specific calibration standards that it considered to be the "best." (DTX 1701; DTX 999A at TEV001222421-RC; DTX 3510 at TEV001116323.)

Moreover, "the chemical arts have long been acknowledged to be unpredictable." *Boston Sci. Corp. v. Johnson & Johnson, Inc.*, 679 F. Supp. 2d 539, 557 & n.36 (D. Del. 2010) (citing *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir. 1983), *aff'd*, 647 F.3d 1353 (Fed. Cir. 2011)). There is no prior art that provides any specific guidance on making the claimed invention, because the claimed molecular weight ranges are relative to the SEC standards chosen by the patentees, which were not disclosed. And Teva introduced no literature at trial and cites no literature here that describes how to overcome the difficulties associated with molecular weight analysis of a material as complex as copolymer-1. Dr. Wall specifically rebutted Dr. Grant's testimony that the cited publications were useful for the molecular weight determination of copolymer-1. (Sept. Tr. 1820:25-1821:19.)

Finally, Sandoz presented numerous documents at trial showing the highly discrepant results that one would obtain when attempting to measure the molecular weight of copolymer-1 using different methods and different SEC standards, and Sandoz presented extensive testimony from Dr. Scandella and Dr. Wall regarding the undue experimentation required to reproduce the claimed invention. (*See, e.g.*, Sept. Tr. 1227:21-1228:11; 1273:13-1274:3 (Scandella); 1764:18-1765:25; 1825:11-19 (Wall); Sandoz's Opening FFCOL ¶¶ 72-78, 85-114, 123-132.)

512. Thus, the trial evidence showed that the person of skill would have addressed the molecular weight issue armed with an extensive and well-developed body of scientific literature addressing SEC. The literature provided significant guidance with respect to both self-standards and universal calibration. There was, moreover, no evidence that the molecular weight determination of copolymer-1 poses any particular or unusual difficulties. In such situations, there is no need for a patent specification to provide extensive discussion of a technique that was well-known and thoroughly described in the prior art. *Hybritech Inc.*, 802 F.2d at 1384 ("[A] patent need not teach, and preferably omits, what is well known in the art."); *see also Monsanto Co.*, 459 F.3d at 1338; *Telectronics, Inc.*, 857 F.2d at 785. The patent specification's reference to a calibrated gel filtration column would be sufficient guidance for a person of skill in the art to accurately determine the average molecular weight and molecular weight distribution of a copolymer-1 sample in view of the teaching and guidance provided by the prior art.

Sandoz's Response:

See Sandoz's Response to ¶ 511, which is incorporated by reference. *See also ALZA*, 603 F.3d at 941 (A patentee "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification."); *Genentech*, 108 F.3d at 1366 ("[W]hen there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.").

(iii) The Quantity of Experimentation is Undue

513. The first *Wands* factor similarly supports the conclusion that the claims of the patents-in-suit are enabled. Dr. Grant testified at trial that a person of skill in the art could have accurately determined the average molecular weight or molecular weight distribution of a

copolymer-1 sample based on the patent disclosure without undue experimentation. (Sept. Tr. (Grant) 1422:9-14.) Dr. Grant's testimony was based on the teachings of the patents-in-suit in view of the guidance provided by the prior art scientific literature on SEC generally and on both self-standards and universal calibration. (Sept. Tr. (Grant) 1422:9-14.)

Sandoz's Response:

The term "accurately" is not defined in this paragraph or in the cited testimony, and to the extent Teva contends that an "accurate" molecular weight of copolymer-1 means its absolute value, Teva is wrong. (Sept. Tr. 1292:21-1293:1 (Scandella); 1825:1-4 (Wall).) Sandoz presented numerous documents at trial showing the highly discrepant results that one would obtain when attempting to measure the molecular weight of copolymer-1 using different methods and different SEC standards, and Sandoz presented extensive testimony from Dr. Scandella and Dr. Wall regarding the undue experimentation required to reproduce the claimed invention. (*See, e.g.*, Sept. Tr. 1227:21-1228:11; 1273:13-1274:3 (Scandella); 1764:18-1765:25; 1825:11-19 (Wall); Sandoz's Opening FFCOL ¶¶ 72-78, 85-114, 123-132.) Teva introduced no literature at trial and cites no literature here that describes how to create self-standards or use universal calibration for a material as complex as copolymer-1. *See* Sandoz's Responses to ¶¶ 451, 454, 489, 497, which are incorporated by reference.

No amount of experimentation or level of skill would remedy Teva's inadequate disclosure of molecular weight methodology, because the patents do not even teach the starting point, *i.e.*, the SEC calibration standards and how to measure the molecular weight of those standards. (Sept. Tr. 1227:21-1228:11 (Scandella); 1764:18-1765:25 (Wall).) Persons skilled in the art are left to choose from a variety of commercial standards, or develop their own set of standards and choose one of many methods to obtain the necessary, independent molecular weight values for those self-standards. (DTX 3581 at 19; Sept. Tr. 1293:15-1295:1.) Such experimentation may have taken "several years" and would have been far from routine. (Sept.

Tr. 1227:21-1228:11; 1291:18-25 (Scandella).) That fact alone warrants a finding of undue experimentation; indeed, the Federal Circuit and its predecessor courts have found undue experimentation in cases involving much less effort than what is required here. *See, e.g., White Consol. Industries, Inc. v. Vega Servo-Control, Inc.*, 713 F.2d 788, 791 (Fed. Cir. 1983) (18 months to two years of effort is undue experimentation); *In re Ghiron*, 442 F.2d 985, 992 (C.C.P.A. 1971) (period of "many months or years...does not bespeak of a routine operation but of extensive experimentation and development work"); *In re Brandstadter*, 484 F.2d 1395, 1406-07 (C.C.P.A. 1973) (same). But even at the end of that process, the molecular weight results for the copolymer-1 self-standards would vary widely, depending on the method chosen, confounding any attempt to reproduce the claimed invention. (*E.g.*, DTX 3137 at TEV000290819.)

Because molecular weight results obtained by SEC are always relative to the standards used, one would have no assurance that the molecular weight values obtained for a set of copolymer-1 samples could be compared to those claimed in the patents, which are based on unknown standards. (Sept. Tr. 1213:17-24; 1221:19-25 (Scandella); 1825:5-19 (Wall).) For this reason, the patent does not teach how to make "the same" copolymer-1 described and claimed in the patents, as required by 35 U.S.C. § 112. The copolymer-1 scientists and Teva consultants recognized the importance of using the same molecular weight procedures. (*See, e.g.*, DTX 3565 at 164:10-15 (Arnon); July Tr. 343:24-344:4 (Arnon); DTX 3568 at 196:11 (Krull); DTX 4017 at 103:17-104:25 (Gad).) Moreover, in its Citizen Petition, Teva explained why using exactly the same process is so essential: "[E]ven the most minor changes in the manufacturing of glatiramer acetate-and in the molecular weight distribution of the resulting product-will produce a new

molecular entity ('NME') with a significantly different potency and safety and efficacy profile." (DTX 1738 at KRULL0000034.)

514. Sandoz offered the testimony of Dr. Scandella, who testified that the use of self-standards would be a major research project (Sept. Tr. (Scandella) 1251:13-1252:9), and Dr. Wall, who testified that a person of skill in the art would give up trying to determine the molecular weight of copolymer-1 after attempting to use globular protein standards. (Sept. Tr. (Wall) 1767:10-1770:22.)

Sandoz's Response:

Dr. Scandella testified that making and characterizing the molecular weights of copolymer-1 self-standards in 1994 would have been a major research project. (Sept. Tr. 1251:13-1252:9 (Scandella).) Dr. Wall testified that if he had been asked to determine the molecular weight of a copolymer-1 sample in 1994 in accordance with the single-sentence description in the asserted patents, he would have first tried SEC calibrated with globular protein standards. (Sept. Tr. 1767:10-1769:6 (Wall).) Then he would have consulted any literature on copolymer-1, which would have led him to try ultracentrifugation. (*Id.* at 1769:7-20.) After that, he would have "found another absolute method of molecular weight determination and tried that." (*Id.* at 1770:3-5.) At that point, Dr. Wall would have considered self-standards and would have concluded that measuring the molecular weight of copolymer-1 according to the patents was "an insoluble problem." (*Id.* at 1770:18-22.)

515. Dr. Wall admitted that he personally stopped using SEC after 1965 and that he

has never used SEC to determine average molecular weights of a mixture of polypeptides such as copolymer-1. (Sept. Tr. (Wall) 1758:21-1759:10, 1759:20-1760:13.) Moreover, Dr. Wall does not have any publications that describe the use of SEC to measure the molecular weight of a polydispersed mixture of polypeptides. (Sept. Tr. (Wall) 1758:4-12.) In fact, despite having testified as an expert in several litigations, Dr. Wall has never been proffered as an expert in SEC. (Sept. Tr. (Wall) 1760:14-17.)

Sandoz's Response:

Dr. Wall testified that 1965 was the *first* time he used SEC. (Sept. Tr. 1749:13-17; 1758:21-25.) Since Dr. Wall joined UCLA in 1972, SEC has been "a pretty continuous technique, both for preparative uses and for molecular weight determinations, up at least until the '90s, late '90s" in his laboratory. (*Id.* at 1751:4-16.) Dr. Wall has also supervised the use of SEC as part of his consulting practice in private industry. One of the companies for whom he has consulted is FMC Bioproducts, "a manufacturer and developer of innovative separations and molecular weight determination materials for columns." (*Id.* at 1752:19-1753:5.) Dr. Wall has supervised "at least 150" researchers on the use of SEC in his laboratory and also teaches a course at UCLA that includes SEC. (*Id.* at 1754:11-1755:6.)

516. There is no evidence to support these opinions offered by Drs. Scandella and Wall, but even if significant experimentation were required that would not mandate the conclusion that the amount of experimentation was "undue." *Falko-Gunter Falkner*, 448 F.3d at 1365 (finding claims to a vaccine were enabled, where the skill level in the art was high, and agreeing with the BPAI that "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered 'undue' in this art").

Sandoz's Response:

Sandoz presented numerous documents at trial showing the highly discrepant results that one would obtain when attempting to measure the molecular weight of copolymer-1 using different methods and different SEC standards, and Sandoz presented extensive testimony from Dr. Scandella and Dr. Wall regarding the undue experimentation required to reproduce the claimed invention. (*See, e.g.*, Sept. Tr. 1227:21-1228:11; 1273:13-1274:3 (Scandella); 1764:18-1765:25; 1825:11-19 (Wall); Sandoz's Opening FFCOL ¶¶ 72-78, 85-114, 123-132.)

"[A] specification need not disclose what is well known in the art. However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure." *Genentech*, 108 F.3d at 1366 (internal citation omitted). In other words,

Teva "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *ALZA*, 603 F.3d at 941. As the *Genentech* court explained, "omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art." *Genentech*, 108 F.3d at 1366.

The absence in the specification of any information on the SEC calibration standards to be used for the molecular weight analysis of copolymer-1, and the absence of the method by which the molecular weights of any self-standards are to be measured, are not "minor details." *Id*. That information is the "specific starting material" necessary to practice the claimed invention, and without it, undue experimentation is required. *Id.* (Sept. Tr. 1227:21-1228:8; 1273:13-1274:3 (Scandella), 1764:18-1765:25; 1825:11-19 (Wall).) Dr. Grant's testimony that one of ordinary skill in the art would know how to calibrate the SEC column to practice the claimed invention based on the one-sentence disclosure in the patents, (Sept. Tr. 1397:20-1398:1), is nothing more than a bare assertion that "all the disclosure related to the process is within the skill of the art," an approach that the Federal Circuit has specifically rejected. *Genentech*, 108 F.3d at 1366.

Teva's reliance on *Falkner* is misplaced. In that case, the patent contained an "extensive disclosure" describing the experimentation needed to practice the claimed invention. *Falkner*, 448 F.3d at 1365. In addition, prior patent applications "provided five detailed working examples" related to the invention. *Id*. at 1364. Neither of these is present here.

517. Moreover, the only evidence that Defendants' experts rely on in support of these opinions are documents showing Teva's early work on its copolymer-1 product. Evidence of what Teva's scientists did to develop and submit a commercial product to the FDA in the late 1980s and throughout the 1990s is not probative of what a person of skill in the art of the patents-in-suit would have done or understood in 1994 unless Defendants affirmatively establish that the scientists working at Teva were, in fact, people of ordinary skill in the art of SEC. *Johns Hopkins Univ.*, 152 F.3d at 1360 (holding that evidence of efforts of inventor's laboratory was insufficient as a matter of law because of failure to show that persons working in laboratory were of ordinary skill in the art). Defendants offered no evidence that the scientists working at Teva had the experience in SEC of a "persons of ordinary skill in the art," as defined by the experts in this case.

Sandoz's Response:

Dr. Scandella and Dr. Wall based their opinions on their experience performing and supervising size exclusion chromatography, their experience working in or consulting for the pharmaceutical industry, the literature that was available in 1994, and on actual copolymer-1 molecular weight data from a wide variety of analytical methods and SEC standards, including information from Teva documents. (*See, e.g.*, Sept. Tr. 1228:2-7; 1228:24-1225:2; 1250:7-18; 1273:19-1274:3; 1290:16-1291:1; 1293:3-7 (Scandella); 1800:13-1801:6; 1811:16-1812:22;1820:25-1821:19 (Wall); *see also* Sandoz's Opening FFCOL ¶¶ 40-162.)

Sandoz has presented extensive evidence that Teva's scientists and consultants were persons of ordinary skill in the art in the relevant time period. (Sandoz's Opening FFCOL ¶ 73-76.) Dr. Grant admitted at trial that the scientists at the Weizmann Institute and at Teva have more experience than he does in attempting to measure the molecular weight of copolymer-1. (Sept. Tr. 1478:16-1479:12.) Moreover, Teva's 1987-1998 documentation of its effort to characterize the molecular weight of copolymer-1 is probative of the complexities of copolymer-1 and the disparate molecular weight results one would have obtained in this timeframe, regardless of whether each individual Teva scientist and consultant was a person of ordinary skill in the art as defined in this case. *See Novo Nordisk*, 424 F.3d at 1362; *AK Steel*, 344 F.3d at 1244-45; *Enzo Biochem*, 188 F.3d at 1372-73. The *Johns Hopkins* court did not hold that the

data obtained by scientists in patentee's laboratory should be disregarded. Nor did the court hold that expert testimony concerning what one of ordinary skill in the art would have done at a certain point in time could not be informed by what those in the patentee's laboratory actually did. In addition, the *Johns Hopkins* court rejected the defendant's reliance on the work in patentee's laboratory because defendant "produced *no evidence* concerning the level of skill of those individuals" working in the lab. *Johns Hopkins*, 152 F.3d at 1360 (emphasis added). Here, by contrast, Sandoz has produced ample evidence to demonstrate that Teva scientists and consultants were persons of at least ordinary skill in the art. (Sandoz's Opening FFCOL ¶¶ 73-76.) Dr. Scandella confirmed that "Teva did what a person of average skill in the art would have done in 1994." (Sept. Tr. 1290:16-20 (Scandella).)

518. The only evidence of record identified by Defendants' experts suggests that there were no people with the requisite training and experience in SEC of a "person of ordinary skill in the art" working at Teva at the time of the work relied on by Defendants. There is likewise no evidence that the Teva employees working to measure the molecular weight of copolymer-1 at the beginning of the project were familiar with all of the prior art. Defendants identified issues with Teva's development beginning in 1987. When asked, the only person that Sandoz's' expert Dr. Scandella could point to as potentially being a person of skill in the art of SEC was Dr. Alexander Gad, but the evidence of record shows that Dr. Gad did not start working at Teva until 1989 (Sept. Tr. (Scandella) 1301:10-25; DTX 4016 (Gad Dep. Nov. 10, 2009) at 12:10-13), two years after Teva developed its molecular weight determination method using self-standards. (Sept. Tr. (Grant) 321:6-322:3, 322:9-324:11; DTX 3275 at TEV000304995; Sept. Tr. (Grant) 324:12-325:13, 1450:15-18, 1451:23-25, 1452:1-13; Sept. Tr. (Scandella) 1307:22-1308:2; Sept. Tr. (Wall) 1828:21-1829:5; DTX 1762 at TEV003017831.) Thus, the Teva work relied on by Defendants is irrelevant to the question of enablement as a matter of law. *See e.g.*, *Johns Hopkins Univ*, 152 F.3d at 1360.

Sandoz's Response:

Following the preliminary work in 1987, the results of which were abandoned, Teva continued to develop its method for estimating the molecular weight of copolymer-1 until at least 1998, when it switched to synthetic peptide markers. (Sandoz's Opening FFCOL ¶¶ 88-116.) Dr. Gad played a substantial role in that development. (*See, e.g.*, DTX 4016 at 29:16-24; DTX 3540.) Moreover, Dr. Scandella was not asked to identify every copolymer-1 scientist he

believed was a person of ordinary skill in the art. Nonetheless, in addition to naming Dr. Gad, he specifically identified Teva's consultant Dr. Krull and the scientists at W.R. Grace as persons of at least ordinary skill in the art. (Sept. Tr. 1238:10-19; 1341:3-5.) As in *Enzo*, "it defies common sense that [Teva] would waste valuable resources conducting experiments...had [it] not believed that [its] research associates possessed sufficient skill to perform them." *Enzo*, 188 F.3d at 1374. And there were many other Teva and Weizmann Institute scientists who were persons of ordinary skill in the art during Teva's development of its molecular weight method, including Dr. Michael Sela, Dr. Ruth Arnon, Dr. Irit Pinchasi, and Dr. Haim Varkony. (Sandoz's Opening FFCOL ¶ 73.) *See* Sandoz's Response to ¶ 517, which is incorporated by reference.

519. Even assuming that evidence of Teva's work on copolymer-1 were relevant to the issue of enablement, Defendants have misinterpreted the evidence. The evidence presented at trial shows that the first copolymer-1 SEC molecular weight determination method developed at Teva in 1987 utilized copolymer-1 self-standards, and that the development took only a matter of weeks. (DTX 4022 (Varkony Dep.) at 110:2-9.) The evidence also shows that Teva continued to use self-standards to measure the molecular weight of copolymer-1 from 1987 through the filing of the NDA in 1995 and approval of the NDA for Copaxone® in 1996. (Sept. Tr. (Grant) 1462:24-1463:4; Sept. Tr. (Wall) 1829:6-9.) None of the documents relied on by Defendants' experts demonstrate that Teva had any difficulty developing a method to measure the molecular weight of copolymer-1 using SEC. To the contrary, to the extent that evidence of Teva's work is relevant to the enablement issue, it demonstrates that the use of SEC to determine the peak molecular weight of copolymer-1 was a relatively straightforward process and supports a determination that the claims are enabled. *In re Wands*, 858 F.2d at 739-740 (finding no undue experimentation after analyzing initial efforts of inventor).

Sandoz's Response:

Teva brazenly misrepresents the evidence in the record by claiming that "*None of the documents* relied on by Defendants' experts demonstrate that Teva had *any difficulty* developing a method to measure the molecular weight of copolymer-1 using SEC." At trial, Sandoz presented document after document showing the highly discrepant results that Teva and its consultants got when attempting to measure the molecular weight of copolymer-1 using different

SEC standards and when attempting to measure the molecular weight of copolymer-1 self-standards using different methods. (*See* Sandoz's Opening FFCOL ¶¶ 77-114.)

Teva's suggestion that developing an acceptable calibration method for copolymer-1 took only several weeks ignores the overwhelming evidence to the contrary that was presented at trial. As noted above, Teva omits the very next lines of Dr. Varkony's testimony:

> Q. Is it your testimony that it only took several weeks for Teva to figure out how to calibrate for determination of molecular weight of Copolymer-1?
>
> A. I have to check the records when we started and until we established the formal methodology. So I cannot say exactly if it is several weeks or more. I don't have the quantitative value.

(DTX 4022 at 110:10-18.) A review of the Teva "records" reveals the fallacy of Dr. Varkony's testimony and Teva's argument. Those records demonstrate that Teva engaged in extensive experimentation for at least *eleven years*, i.e., 1987 to 1998, to find an acceptable SEC calibration standard and an acceptable method for measuring the molecular weights of its copolymer-1 self-standards. *See* Sandoz's Response to ¶ 477, which is incorporated by reference. Teva first tried globular proteins for column calibration, not self-standards. *Id.* And when Teva did try self-standards, it could not settle on a single method of measuring the molecular weights of those standards. In 1992, Teva abandoned its initial method of characterizing the standards by viscometry and introduced a new method that characterized the molecular weights of the standards by MALLS. (DTX 1701.) According to Teva, the MALLS-based method "assures a better determination" of molecular weight than the prior methods. (DTX 3510 at TEV001116323.) Thus, it is incorrect to suggest that Teva settled on self-standards in 1987 and continued to use those self-standards through the approval of the NDA in 1996.

By the filing date of the patents, Teva still had not figured out how to resolve the discrepant molecular weight results for copolymer-1, As Dr. Krull stated in 1995: “At issue here is the observation that COP-1 results in terms of MW and MW distributions appear to vary from method to method and sample to sample,” and that unless certain problems were addressed and overcome, “we can never have comparable results.” (DTX 1744 at TEV001017877-78; Sept. Tr. 1512:13-1513:3 (Grant).)

In 1996, Dr. Varkony and Teva were still engaged in “speculation on MW determination of COPOLYMER-1.” (DTX 1706 at TEV001013050.) According to Dr. Varkony: “The MW-determinations by MALLS carried out so far in TEVA using three different SEC columns give always considerably higher than the values determined by SPP or by ultracentrifugation.” (*Id.* at TEV001013038.) He concluded: “We don’t know how to relate this results [sic] to the existent specifications for copolymer 1.” (*Id.* at TEV001013040.) MALLS was the analytical method that Teva was using between 1992 and 1998 to measure the molecular weight of its copolymer-1 self-standards and is the method used to create the “calibrated gel filtration column” referenced in the asserted patents. (DTX 1701 at TEV001202498; Sept. Tr. 1521:24-1522:4; 1573:19-22 (Grant); DTX 4016 at 48:14-49:14, 50:20-52:23 (Gad).)

[redacted]

[redacted]

In 1996, Teva found that "[t]he numeric average molecular weight Mn obtained by the MALDI-ToF experiments is much lower than the value determined by the chromatographic method with MALLS detection (~4000 Da versus ~10,000 Da) or versus ultracentrifugation (~7000 Da)." (DTX 3137 at TEV000290819.) As Dr. Wall explained at trial, "even at this point well into almost a decade of extensive molecular weight characterization, this new method didn't match any of the previous determinations." (Sept. Tr. 1805:5-7 (Wall).) Teva concluded that "[t]he differences are due to the experimental bias of the analytical technique and how data are calculated and presented. Therefore, *it should be explicitly stated by which analytical method the molecular weight data were obtained*." (DTX 3137 at TEV000290820 (emphasis added).)

According to the Gad marker '580 patent, as of September 1998, "a need exists for molecular weight markers useful as standards for determining the molecular weight distribution of copolymer compositions contemplated by the invention." (DTX 3540 at col. 3:47-50.) According to the '580 patent, calibrating a Superose 12 column with the peptide markers for copolymer-1 molecular weight analysis "has several advantages over the currently used glatiramer acetate molecular weight markers" including "consistency among the various preparations of each batch" and "improved accuracy in molecular weight determination." (DTX 3540 at col. 21:63-22:4.)

Thus, Teva is mistaken that its work "demonstrates that the use of SEC to determine the peak molecular weight of copolymer-1 was a relatively straightforward process."

(iv) <u>The Patents Contain No Relevant Working Examples</u>

520. Turning to the third *Wands* factor, the patents-in-suit contain working examples. First, Example 1 of the patent discloses the use of SEC to determine the average molecular weight of copolymer-1 samples. (PTX 1, col. 2:51–3:18.) The example discloses that the

molecular distribution of the copolymer-1 samples was determined using a calibrated size exclusion chromatography column. (PTX 1, col. 3:9-18.)

Sandoz's Response:

The patents provide only one sentence on how to determine the molecular weight of copolymer-1: "The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12)." (PTX 1, col. 3:6-8.) There are no working examples on how to calibrate the SEC column to make the same copolymer-1 that is claimed. The one-sentence molecular weight disclosure is particularly egregious given that Teva had possession of detailed molecular weight calibration procedures, including specific calibration standards that it considered to be the "best." (DTX 1701; DTX 999A at TEV001222421-RC; DTX 3510 at TEV001116323.)

521. Momenta has acknowledged that if one were to follow of the disclosure of patents-in-suit, the resulting compound would be copolymer-1. Specifically, Dr. Mani Iyer, who developed the Momenta process, acknowledged that the process for making copolymer-1 used by Momenta tracks the steps disclosed and claimed in claim 1 of the '808 patent and results in copolymer-1 with an average molecular weight of 5-9 kilodaltons. (PTX 960 (Iyer Dep.) at 146:12-151:22.) Mylan's expert Dr. Hurwitz also testified that the methods described in the patents would enable a person of ordinary skill in the art to make a batch of copolymer-1. (PTX 959 (Hurwitz Dep.) at 130:15-20.) Thus, the working examples found in the patents-in-suit support a finding of enablement. *See e.g.*, *In re Wands*, 858 F.2d at 740 (finding no undue experimentation, where disclosure presents working examples).

Sandoz's Response:

The cited testimony does not address Momenta's attempts to calibrate the SEC column for molecular weight determination. The evidence in the record shows that, upon reading the patent specification, Momenta scientists first calibrated the SEC column with commercially available globular protein standards, because it was "the approach disclosed in US Patent 6,939,539 B2 (listed in the Orange Book for Copaxone®)." (PTX 236 at MMT00638170; Sept. Tr. 1243:4-13 (Scandella).) *See* Sandoz's Opening FFCOL ¶¶ 143-144. Momenta's approach to SEC calibration for copolymer-1 was the same approach that one of ordinary skill in the art

would have taken in 1994. (Sept. Tr. 1243:20-25; 1245:11-14 (Scandella).) The *Johns Hopkins* case, on which Teva relies, held that "[a] party who wishes to prove that the claims of a patent are not enabled by means of a failed attempt to make the disclosed invention must show that the patent's disclosure was followed." *Johns Hopkins*, 152 F.3d at 1360. By citing Momenta's failed attempt to make the claimed copolymer-1 using protein standards, Sandoz has made that showing.

Momenta ultimately developed a method for determination of the molecular weight of copolymer-1 using the "reference listed drug," *i.e.*, Copaxone, as the starting point and "after considerable work." (Sept. Tr. 1314:5-14 (Scandella).) Dr. Scandella testified about the significance of having the reference listed drug available to define the molecular weight target:

> Q. What is the significance of having that [reference listed drug]?
>
> A. Well, the reference listed drug is a standard for you. You know the molecular weight data for that standard from the reference listed drug information, and you can use that information to calibrate your method. Momenta scientists have indicated it would have been very difficult to develop that method without that reference material.

(Sept. Tr. 1336:1-8 (Scandella).) Indeed, former Momenta scientist Dr. Corrine Bauer testified that with respect to the molecular weight determination of copolymer-1, "[t]he first product we analyzed was a reference listed drug." (PTX 956 at 43:6-7.)

Momenta scientists also had the peptide standards from the Gad patents and "were able to use the approach used in the Gad patents to create their own peptide standards. That material, that information would not have been available, of course, in 1994 or 1995." (Sept. Tr. 1336:9-15 (Scandella).) Dr. Bauer confirmed the importance of the Gad patents in this regard:

> Q. Now, when you started working on the accurate method of determining the molecular weight, what technique did you use?

> A. We evaluated a lot of things. We really tried to understand what the innovator was doing. And it's not before the Gad patents that we got some light on how the molecular weight -- what type of molecular weight, you know, the label -- the label was referring to and how it was -- this result was obtained.

(PTX 956 at 55:13-24.) Therefore, Momenta was successful in creating a generic glatiramer acetate with an average molecular weight of 5-9 kilodaltons in spite of the meager patent disclosure, not because of it.

In addition, Teva's citation to Mylan's expert is misplaced, because the ability to "make a batch of copolymer-1" is not the same as the ability to make copolymer-1 with the claimed molecular weight ranges using the same calibration standards used by the patentees. The patents do not disclose how to make such copolymer-1. (Sept. Tr. 1825:5-19 (Wall).)

(v) <u>The Nature of the Invention and Breadth of the Claims</u>

522. Finally, the patents-in-suit are directed to a lower molecular weight form of copolymer-1 for the treatment of multiple sclerosis. High molecular weight copolymer-1 was known in the prior art and the concepts of molecular weight and the measurement of molecular weight using size exclusion chromatography were well-known in 1994. As discussed above, there was a significant quantity of scientific literature describing SEC and its use for determining the molecular weight of polydisperse polymers such as copolymer-1. There is nothing about the nature of the invention claimed in the patents-in-suit that supports a finding that the claims are not enabled.

<u>*Sandoz's Response:*</u>

Teva is asserting composition and method claims relating to copolymer-1, which is a polypeptide mixture of extreme complexity and heterogeneity. (July Tr. 28:8-13 (Pinchasi); DTX 1744 at TEV1017878.) Copolymer-1 contains molecules of variable length and structure, which means there will be variation in both molecular weight and behavior in an SEC column. (Sept. Tr. 1200:5-18 (Scandella); Sept. Tr. 1812:14-22 (Wall).) Teva introduced no literature at trial and cites no literature here that describes how to overcome the difficulties associated with molecular weight analysis of a material as complex as copolymer-1. Dr. Wall specifically

rebutted Dr. Grant's testimony that the cited publications were useful for the molecular weight determination of copolymer-1. (Sept. Tr. 1820:25-1821:19.) Nor could any prior art provide specific guidance on making the claimed invention, because the claimed average molecular weights and distributions are relative to the SEC standards chosen by the patentees, which were not disclosed. *See* Sandoz's Responses to ¶¶ 451, 454, 466 and 467 and Sandoz's Opening FFCOL ¶ 160, which are incorporated by reference.

523. Based upon a review of the evidence presented at trial, and a consideration of the *Wands* factors, there is no evidence that the claims of the patents-in-suit are overbroad, or that the breadth of the claims supports a finding of nonenablement. A person of skill would understand the meaning and scope of the claims of the patents-in-suit and was able to properly construe each of the disputed claim terms. (Claim Construction Order at 3.)

Sandoz's Response:

See Sandoz's Opening FFCOL ¶¶ 154-170, which are incorporated by reference.

524. In sum, Defendants have failed to show that application of *any* of the *Wands* factors leads to a conclusion of lack of enablement. To the contrary, the evidence presented at trial demonstrates that a person of skill in the art would have been able to make and measure the molecular weight of copolymer-1 without undue experimentation.

Sandoz's Response:

See Sandoz's Opening FFCOL ¶¶ 154-163, which are incorporated by reference.

VIII. FINDINGS OF FACT AND CONCLUSIONS OF LAW RELATING TO RELATING TO THE BEST MODE DEFENSE

(Teva Proposed Findings of Fact and Conclusions of Law ¶¶ 525-557)

Sandoz's Response:

Sandoz incorporates by reference the Mylan Responses to Teva's ¶¶ 525-557.

IX. FINDINGS OF FACT AND CONCLUSIONS OF LAW RELATING TO DEFENDANTS' INEQUITABLE CONDUCT DEFENSE

558. Defendants allege that Dr. Pinchasi committed inequitable conduct by failing to submit to the PTO a single page of data containing results of toxicity testing for thirteen batches of copolymer-1 (the "April 1994 Data Table") and failing to inform the PTO of her alleged reservations about the RBL degranulation test. As set forth below, Defendants have failed to

carry their burden of proving inequitable conduct by clear and convincing evidence.

Sandoz's Response:

Teva's summary of Sandoz's inequitable conduct defense is overly simplistic. Dr. Pinchasi's inequitable conduct stems from her overall failure to disclose information to the PTO that would have caused the PTO not to allow the claims of the patents-in-suit. Her failure to provide the "April 1994 Data Table" is representative of her failure to produce toxicity data that was inconsistent with the toxicity data she did provide to the PTO. Had she disclosed that data, or any other complete picture of the toxicity data to the PTO, the PTO would not have allowed the claims of the patents-in-suit to issue. Similarly, but for Dr. Pinchasi's "alleged reservations" regarding the RBL test (*e.g.*, (DTX 999A at TEV001222393-394-RC ("It is clear from this table that the RBL system is inconsistent in its reproducibility, and both inter-assay and intra-assay large variations were observed. . . . We thus feel that this assay can not be properly controlled.")), the PTO could not have any confidence that the patents-in-suit showed unexpectedly lower toxicity than the prior art and would not have issued the claims.

A. Legal Principles

559. To prove inequitable conduct, the accused infringer must establish by clear and convincing evidence that the patent applicant (1) made an affirmative misrepresentation of material fact, failed to disclose material information, or submitted false material information and (2) did so with the intent to deceive the PTO. *Cancer Research Tech. Ltd. v. Barr Labs, Inc.*, 625 F.3d 724, 732 (Fed. Cir. 2010); *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1365 (Fed. Cir. 2008).

560. Intent and materiality are separate elements that must be proven independently by clear and convincing evidence. *Therasense, Inc. v. Becton, Dickinson & Co.*, No. 2008-1511, 2011 WL 2028255, at *10 (Fed. Cir. May 25, 2011) (*en banc*).

561. The Federal Circuit's *en banc* decision in *Therasense* explicitly "tighten[ed] the standards for finding both intent and materiality in order to redirect a doctrine that has been overused to the detriment of the public." *Id.* at *9.

562. With respect to materiality, the Court held that a "but-for" standard applies. *Id.* at 11. In order to assess materiality, "the court must determine whether the PTO would have

allowed the claim if it had been aware of the undisclosed reference." *Id.*

563. The Court recognized a narrow exception to the requirement of proving but-for materiality that applies only in "extraordinary circumstances" that amount to "affirmative acts of egregious misconduct" such as the "filing of an unmistakably false affidavit." *Id.* at *12-13. The mere withholding of information or prior art references, however, cannot, as a matter of law, constitute an "affirmative act of egregious misconduct." *Id.* at *12.

Sandoz's Response:

This is a misstatement of the law. When discussing the "affirmative acts of egregious misconduct prong," the en banc Court in *Therasense* noted: "Because neither mere nondisclosure of *prior art references* to the PTO nor failure to mention *prior art references* in an affidavit constitutes affirmative egregious misconduct, claims of inequitable conduct that are based on such omissions require proof of but-for materiality." (*Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1292-93 (Fed. Cir. 2011) (*en banc*) (emphasis added).) This limitation applies only to the nondisclosure of "prior art references." Teva is attempting to broaden the exception to the exception so as to exclude "information" in addition to "prior art." The Federal Circuit did not exclude the non-disclosure of all "information." The Federal Circuit's distinction makes sense, as PTO examiners have at least a chance of discovering withheld prior art as part of their duties to search for prior art. Examiners have no chance of finding the type of information withheld by Dr. Pinchasi (unfavorable internal data that is inconsistent with the favorable internal data presented to the PTO and the company's internal doubts about the scientific arguments it made in support of patentability). Accordingly, Dr. Pinchasi's withholding of "information" can be an "affirmative act of egregious misconduct."

564. Undisclosed information that is consistent with statements, data, or representations in a patent is cumulative and therefore cannot be material. *See Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1375-77 (Fed. Cir. 2006).

Sandoz's Response:

This statement of law should not be included in the conclusions of law because it is unnecessary to deciding the present case and it may not be a correct statement of the law. The rule that "cumulative" information is not material comes from the PTO's Rule 56. 37 C.F.R. § 1.56(b) ("Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application."). The Federal Circuit, in *Therasense*, held, "[t]his court does not adopt the definition of materiality in PTO Rule 56." (*Therasense*, 649 F.3d at 1293.)

565. With respect to intent, the *Therasense* Court found that an accused infringer must prove "that the applicant knew of the reference, knew it was material, and made a deliberate decision to withhold it." *Therasense*, 2011 WL 2028255, at *9. A specific intent to deceive must be the "single most reasonable inference" able to be drawn from all the evidence. *Id*. at *10 (quoting *Star Scientific, Inc.*, 537 F.3d at 1366). "Indeed, the evidence 'must be sufficient to *require* a finding of deceitful intent in light of all the circumstances.'" *Id.* (quoting *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 873 (Fed. Cir. 1988)). Where multiple, reasonable inferences could be drawn from the evidence, an intent to deceive cannot be found. *Id.* (citation omitted).

566. *Therasense* also confirmed that an intent to deceive may not be inferred solely from materiality. A court must weigh the evidence of intent to deceive independently from the evidence of materiality. "Proving that the applicant knew of a reference, should have known of its materiality, and decided not to submit it to the PTO does not prove specific intent to deceive." *Id.* (citing *Star Scientific, Inc.*, 537 F.3d at 1366). A weak showing of intent to deceive *cannot* be overcome with a stronger showing of materiality, or vice-versa. *Id.*

B. Findings of Fact

(i) Dr. Pinchasi's Involvement with the '037 Application

567. On May 24, 1994, Mr. Neil Nachshen, an employee in Teva's Patent Department asked Dr. Pinchasi whether she was aware of any publications related to copolymer-1 that were due for publication. (DTX 1393 (Nachshen Dep. 10/13/10) at 11:22-12:4, 20:22-21:7.) Dr. Pinchasi informed Mr. Nachshen that she believed that a paper was to be published that same day in the Proceedings of the National Academy of Sciences (PNAS). (DTX 1393 (Nachshen Dep. 10/13/10) at 20:22-21:7.)

Sandoz's Response:

[redacted]

568. Mr. Nachshen confirmed the publication date with PNAS at about 4 p.m. local (Israel) time on May 24, 1994. (DTX 1393 (Nachshen Dep. 10/13/10) at 21:16-23:13.) At that point Mr. Nachshen told others at Teva that they should file a patent application that day, to preserve patent rights in foreign (*i.e.*, non-U.S.) jurisdictions. (PTX 11 at TEV000309430-433; DTX 1393 (Nachshen Dep. 10/13/10) at 20:5-20:14.) That application was filed as U.S. serial no. 08/248,037 ("'037 application").

569. The '037 application contains the same Example 2 that appears in the patents-in-suit as described in paragraphs 105-111 above. The '037 application, however, had different claims from the ones that ultimately issued in later applications that resulted in the patents-in-suit. In particular, the '037 application had no claims directed to copolymer-1 with an average molecular weight in any particular range. (July Tr. (Pinchasi) at 131:11-23; PTX 10 at TEV003009937.)

Sandoz's Response:

This statement is false. There is virtually no difference in the originally-filed claims 1, 2, and 4 compared to claims 1 and 8 of the '098 patent. This chart lists, side-by-side, claim 1 of the '098 patent and claims 1-5 of the original application:

Claims 1 and 8 of '098 patent	**Original Claims 1-4 filed May 24, 1994**
1. A copolymer-1 composition comprising a mixture of copolymers of alanine, glutamic acid, lysine and tyrosine, the copolymer species in the mixture being non-uniform with respect to molecular weight and sequence, wherein over 75% of the copolymers in the mixture, on a molar fraction basis, have a molecular weight in the range of 2 kDa to 20 kDa and less than 5% of the copolymers have a molecular weight above 40 kDa, and wherein the composition is suitable for treating multiple sclerosis.	1. Copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons. 2. Copolymer-1 according to claim 1, wherein the composition contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons. 3. Copolymer-1 according to claim 1, wherein the composition contains less than 2.5% of species of copolymer-1 having a molecular

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8. The composition of claim 1, wherein less than 2.5% of the copolymers in the mixture have a molecular weight above 40 kDa. (PTX 9.)	weight of over 40 kilodaltons. 4. Copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa. (PTX 11 at TEV000309445.)

While claim 1 of the ’098 patent includes additional language regarding a requirement that the copolymer-1 include “a mixture of copolymers of alanine, glutamic acid, lysine and tyrosine, the copolymer species in the mixture being non-uniform with respect to molecular weight and sequence,” the Court already construed the word “copolymer-1” to include those limitations. Specifically, the Court construed copolymer-1 to mean “a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively, non-uniform with respect to molecular weight and sequence, which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides.” (Claim Construction Order at 12.) Thus, the inclusion of the extra language in the ’098 patent is merely redundant of the meaning of “copolymer-1” as the term was used in the claims drafted in May 1994. The comparison between the ’098 patent and the original claims is easier when the redundant claim language is deleted:

Claims 1 and 8 of ’098 patent (with deleted surplusage)	**Original Claims 1-4 filed May 24, 1994**
1. A copolymer-1 composition wherein over 75% of the copolymers in the mixture, on a molar fraction basis, have a molecular weight in the range of 2 kDa to 20 kDa and less than 5% of the copolymers have a molecular weight above 40 kDa, and wherein the composition is suitable for treating multiple sclerosis. 8. The composition of claim 1, wherein less than 2.5% of the copolymers in the mixture	1. Copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons. 2. Copolymer-1 according to claim 1, wherein the composition contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons. 3. Copolymer-1 according to claim 1, wherein the composition contains less than 2.5% of

have a molecular weight above 40 kDa. (PTX 9)	species of copolymer-1 having a molecular weight of over 40 kilodaltons. 4. Copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa. (PTX 11 at TEV000309445)

The Court should make these additional findings of fact:

SDZ362. The claims drafted by Dr. Pinchasi and her team on the evening of May 24, 1994 are substantially similar to claims 1 and 8 of the issued ’098 patent.

SDZ363. Teva is wrong that the original claims had “no claims directed to copolymer-1 with an average molecular weight in any particular range.” The original patent application included a claim to “[c]opolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa.” (PTX 11 at TEV000309445 (claim 4); PTX 12 at TEV000309513 (claim 4).)

570. Mr. Nachshen prepared the ’037 application with the assistance of three other Teva employees, Dr. Pinchasi, Dr. Ralph Haber, and Dr. Ilan Schwartz, in consultation with attorneys from the New York City and Washington, D.C. offices of Kenyon & Kenyon LLP. (DTX 1393 (Nachshen Dep. 10/13/10) at 19:6-13, 20:15-17, 21:7-11, 40:25-41:3, 41:8-12; July Tr. (Pinchasi) 116:9-20, 117:6-11.)

Sandoz’s Response:

While some New York City-based Kenyon and Kenyon attorneys of record in this case were also at one point attorneys of record in the prosecution of the patents-in-suit, Teva cannot use its inside knowledge of the facts to support this Court’s findings without waiving attorney-client privilege. The originally filed patent application was signed by David B. Bonahm, who lists a Kenyon & Kenyon address in Washington, D.C. (PTX 11 at TEV000309433.) This, at most, shows that a Washington-D.C. based Kenyon & Kenyon attorney filed the completed

application with the PTO. Mr. Bonahm's fax number listed below his signature block on the same page is (202) 429-0796, which is the same fax number appearing on the original patent application. (PTX 11 at TEV000309437.) The other fax number belonged to "Innovative R&D," which was Neil Nachshen's department at Teva. (*Id.*; PTX 1393 at 13:3-9 (Nachshen).)

571. Although Mr. Nachshen drafted the majority of the '037 application, he relied upon others working with him, including Dr. Pinchasi, to provide technical assistance on the subject matter described and claimed in the patent application. (*See e.g.*, DTX 1393 (Nachshen 10/13/2010 Dep.) at 23:20-24:21, 26:10-23, 26:24-27:19.)

<u>*Sandoz's Response:*</u>

Mr. Nachshen relied on the others working with him to provide much more than "technical assistance." He testified:

> I had no previous knowledge or experience of working with this molecule at all, and I was, therefore, wholly dependent on the other three people that were with me as to what to include in the patent specification.
>
> I could give them some limited advice in terms of being -- having experience as a patent agent, or trained as a patent agent. But in terms of what went in to make the case and what was relevant and what wasn't relevant, that was out of my remit because I didn't make that decision.

(DTX 1394 at 22:6-18 (Nachshen).)

While Mr. Nachshen may have drafted a substantial portion of the original patent application, the inequitable conduct allegations center on Example 2, which was among Dr. Pinchasi's contribution to the application. Dr. Pinchasi, not Mr. Nachshen, actually wrote the words "Example 2B" in the original patent application. (DTX 999A at TEV001222321-RC, TEV001222350-RC; PTX 11 at TEV000309442; July Tr. 150:22-152:17.) Pinchasi, not Nachshen, provided the actual text and data used in Example 2. (July Tr. 155:8-19; 204:12-22.) She reviewed it for accuracy. (July Tr. 205:9-21.)

572. During the preparation of the '037 application on May 24, 1994, Dr. Pinchasi

provided biological data, specifically in vivo and in vitro toxicity data, for potential use in the application. (July Tr. (Pinchasi) 117:6-14, 122:4-7.) She did not, however, make the final decision on which data to include in the '037 application. (July Tr. (Pinchasi) 146:2-5.)

Sandoz's Response:

Dr. Pinchasi's claim that she did not make the final decision on the Example 2 data lacks credibility. The Court should make these additional findings:

SDZ364. Dr. Pinchasi gave the overall order to file the patent application that day. (DTX 1393 at 20:15-17 (Nachshen) (Q. "And do you recall who it was who said essentially, we agree, go file?" A. "Irit Pinchasi."); DTX 1394 at 27:2-28:6.)

SDZ365. Pinchasi provided all the data for Example 2; she physically wrote the header of a subsection in Example 2; and she reviewed Example 2 for accuracy. (DTX 999A at TEV001222321-RC; TEV001222350-RC; PTX 11 at TEV000309442; July Tr. 150:22-152:17, 155:8-19, 204:12-22, 205:9-21.)

SDZ366. Dr. Pinchasi stayed at Teva past midnight to finish the patent application, which was "unusual" for her. (July Tr. 203:18-22.)

SDZ367. None of the other three Teva employees present that evening knew anything about the toxicity data. (July Tr. 145:12-22; DTX 1389 at 28:25-29:6 (Haber); (DTX 1394 at 22:2-18 (Nachshen)).)

573. Dr. Pinchasi had never been involved in preparing a patent application before the night of May 24, 1994. (July Tr. (Pinchasi) 122:24-123:4.)

574. Before the '037 Application was filed on May 24, 1994, Dr. Pinchasi reviewed it and confirmed that it accurately reflected what she knew about the biological toxicity profile of copolymer-1, as measured by the *in vivo* and *in vitro* toxicity tests described in Example 2. (July Tr. (Pinchasi) 129:1-17.)

<u>*Sandoz's Response:*</u>

Dr. Pinchasi testified that Teva's overall toxicity data supported "trends" and "probabilities" that lower molecular weight copolymer-1 is less toxic than higher molecular weight copolymer-1. (*See, e.g.*, July Tr. 59:24-60:24, 246:5-18, 262:7-14.) It lacks credibility for Dr. Pinchasi to say that she could look at the data in the patents and conclude that it showed a "trend." Both Sandoz's expert Dr. Kimber and Teva's expert Dr. Baird agreed that the data provided in Example 2 suggests two "camps" with clear differences, and not merely a trend or probability of lower toxicity at lower molecular weights and vice versa. (July Tr. 401:7-15 (Kimber); July Tr. 601:5-12 (Baird).) Pinchasi is a trained scientist and knows that trends and probabilities cannot be shown with a mere one "toxic" batch with the in vivo mouse test and two "toxic" batches with the in vitro RBL tests.

(ii) <u>The Claims Would Not Have Issued</u>

575. Defendants presented no competent expert evidence at the Inequitable Conduct trial to support a finding that any of the claims in the patents-in-suit would not have issued had the PTO known about the April 1994 Data Table or Dr. Pinchasi's views on the RBL degranulation test.

<u>*Sandoz's Response:*</u>

Sandoz presented substantial evidence in its opening Proposed Findings of Fact establishing that Teva would not have obtained the claims of the patents-in-suit absent a showing that its purported invention showed unexpected results and that, but for Dr. Pinchasi withholding the additional toxicity data and her internal skepticism about the RBL test, the PTO would not have credited the evidence Teva provided showing unexpected results.

576. The only evidence proffered by Defendants was a recitation by Defendants' patent expert Mr. Rzucidlo of various communications between Teva and the PTO during prosecution of the patents-in-suit. None of this prosecution history, however, is relevant to the inequitable conduct claim in this case.

<u>*Sandoz's Response:*</u>

This is nonsense. The evidence includes the testimony of all the witnesses, including those who testified via videotape, the examination and cross examination of Teva's witnesses, and the documents admitted into evidence. One question the Court must answer in the inequitable conduct inquiry is whether the patents-in-suit would have issued but for Teva's withholding of information from the PTO. Sandoz agrees that the prosecution history of the patents-in-suit is not definitive of what would have happened but for Teva's withholding of information. Instead, the Court must determine whether the claims would have issued if the PTO had the withheld information. When making that determination, the Court is not bound to make the same decisions as the Examiner.

577. Under Defendants' theory, the allegedly withheld toxicity information is related to the issue of unexpected results, which is a secondary consideration of non-obviousness. Unexpected results, however, are only relevant once a claim has been demonstrated to be *prima facie* obvious in view of the prior art. There is no evidence that unexpected results were used to overcome a *prima facie* obviousness rejection based on the '550 patent during prosecution.

<u>*Sandoz's Response:*</u>

Teva misstates the law, and there is clear and convincing evidence that Teva made its "unexpected results" arguments to avoid rejections for *prima facie* obviousness. Sandoz need not prove that there was an actual finding of *prima facie* obviousness in the prosecution history to prove inequitable conduct. The inequitable conduct inquiry is necessarily a hypothetical exercise in which the Court is tasked with determining, had Teva not withheld the toxicity information and its internal doubts, would a patent have issued? The Court must go back in time and place itself in the shoes of the Examiner, reading the patent application in the first instance. If the Court holds that the Examiner should have issued a *prima facie* obviousness rejection over the prior art, knowing all the information Teva withheld, then the burden in the hypothetical exercise would have shifted to the patent applicant, Teva, to show unexpected results.

Teva is correct that as a general proposition unexpected results can be used to overcome obviousness rejections. *See, e.g., Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007) (holding that patent owner "failed to show unexpected results that would tend to rebut a prima facie case of obviousness"); *In re Merck & Co.*, 800 F.2d 1091, 1098 (Fed. Cir. 1986) ("A prima facie case of obviousness can be rebutted by evidence of unexpected results."). Teva does not dispute that it made several unexpected results arguments throughout the prosecution of the nine patents-in-suit. (*See* Sandoz Opening FFCOL ¶ 322 and accompanying chart.) Its only argument is that it did not make the arguments in direct response to a *prima facie* obviousness rejection. Teva asks the Court to believe that Teva made all of the "unexpected results" arguments for no reason, as unexpected results cannot be considered in response to anticipation rejections. *See* M.P.E.P. § 2131.04 ("Evidence of secondary considerations, such as unexpected results or commercial success, is irrelevant to 35 U.S.C. § 102 rejections and thus cannot overcome a rejection so based.") (*citing In re Wiggins*, 488 F.2d 538, 543 (CCPA 1973).)

Most of Teva's arguments during the prosecution of the patents-in-suit were in response to anticipation rejections over the '550 patent and the EP '620 patent application. (PTX 12-21; Sandoz Opening FFCOL ¶ 321 and accompanying chart.) But even when it received only anticipation rejections, Teva argued unexpected results anyway because anticipation rejections are essentially obviousness rejections, too. *See Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) ("[A] disclosure that anticipates under § 102 also renders the claim invalid under § 103, for 'anticipation is the epitome of obviousness.'") (*quoting In re Fracalossi*, 681 F.2d 792 (C.C.P.A. 1982)). By making unexpected results arguments in response to anticipation rejections, Teva was cutting off the forthcoming obviousness rejection that could follow the first

anticipation rejection. Because the "unexpected results" arguments were accepted at the same time Teva's anticipation arguments were accepted, the Examiners did not have to issue separate obviousness rejections after Teva overcame its anticipation rejections.

578. The first and only obviousness rejection over the '550 patent occurred during the prosecution of the application that resulted in the '808 patent. (*See* PTX 13 at TEV000304138-144.) In response to that rejection, Teva never cited to the data in Example 2 or argued unexpected results to overcome a *prima facie* obviousness rejection. Instead, the Examiner withdrew the *prima facie* obviousness rejection noting that the '550 patent did "not fairly suggest, teach or disclose the subject matter embodied" by the allowed claim. (PTX 13 at TEV000304148-52, TEV000304156.) Teva thus was not required to rely on unexpected results in order to establish the patentability of the '808 patent. (*See* July Tr. (Rzucidlo) 539:9-14, 539:23-541:21, 547:4-550:10.)

Sandoz's Response:

Teva is wrong. Teva cites a February 14, 1997 Office Action as the "first and only obviousness rejection over the '550 patent." (PTX 13 at TEV000304138, 142.) Teva's counsel made this same misrepresentation to the Court during trial. (July Tr. 488:4-5.) The first obviousness rejection over the '550 patent was nearly two years earlier on June 26, 1995. (PTX 12 at TEV000309546 ("Claims 2-6 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 *as obvious over Teitelbaum et al.* [the '550 patent]." (emphasis added)).)

It is not relevant whether the particular Examiner actually required Teva to argue unexpected results in the hypothetical inquiry. The issue is whether the patent should have issued absent a showing of unexpected results. Sandoz's opening brief explains why the claims of the patents-in-suit are prima facie obvious. (*See, e.g.*, Sandoz Opening FFCOL ¶¶ 212-227.) As Mr. Rzucidlo testified, the *Manual of Patent Examining Procedure* instructs examiners to issue prima facie obviousness rejections when a claim is directed to adjacent or abutting ranges of a particular property. (July Tr. 514:6-515:19; *see generally*, M.P.E.P § 2144.05.)

Even if the law required that Sandoz show that Teva actually made unexpected results arguments following a *prima facie* obviousness rejection, the prosecution history shows that Teva presented unexpected results evidence to the PTO when responding to the obviousness rejection. When responding to the second obviousness rejection over the ’550 patent, Teva argued that the ’550 patent did not “suggest any advantage to obtaining particular molecular weight fractions of copolymer-1 through the claimed method.” (PTX 13 at TEV000304151.) Here, “advantages” refers to lower toxicity corresponding to the lower molecular weight. Mr. Rzucidlo, speaking from the perspective of a former patent examiner, testified that when an applicant describes his invention as “advantageous,” he is saying that it is unexpected over the prior art. (July Tr. 515:24-517:12.) This is consistent with Teva’s internal description of the correlation between molecular weight and toxicity as “advantageous.” Specifically, Dr. Pinchasi testified about a document authored by Mr. Konfino, with the heading, “The Advantageous Molecular Weight,” which described the purported correlation between molecular weight and toxicity. (PTX 708 at TEV000324552; July Tr. 284:5-25.)

(iii) The April 1994 Data Table Was Material

579. The April 1994 Data Table, reproduced below, contains batch numbers, molecular weight, and other information for thirteen batches of copolymer-1. (DTX 999A at TEV001222355-RC; DTX 3149T.)

אצווה מס'	מ.מ. ממוצע	פיק III SELECT B	% שחרור RBL	SAFETY IN VIVO	SKIN IRRITATION *
123-094	6250	41.0	12.4	0/5	N.T
123-090	7300	43.3	21	0/5	14±2.5 (14±1.2)
123-095	8400	40.8	25.6	0/5	11.6±1.5(12±1.2)
04792	9250	43.9	31.3	0/5	13.8±1(14±1.2)
04892	9600	44.2	50.5 (?)	0/5	N.T.
04992	9900	43.9	51.5 (?)	0/5	13.8±1.2(14±1.2)
123-096	10,950	44.2	39.8	0/5	N.T.
04592	11,050	45.3	41.3	0/5	16±1.2(16.4±0.8)
04692	11,900	45.8	41.7	0/5	N.T.
04492	12,150	47	47.6	0/5	18±1.8(17.2±1)
196/2	13,000	45.1	66.9	0/5	16.2±1(17±1.55)
196/1	14,500	44.66	67.8	0/5	15.6±0.8(14.8±1)
186/1	22,000	47.21	60.3	3/5	N.T.

580. Dr. Pinchasi was not sure whether she personally created the April 1994 Data Table, but believes it was one of many such summary tables created during the development of copolymer-1 in order to compare chemical and biological data related to different batches. (July Tr. (Pinchasi) 124:13-125:1.)

Sandoz's Response:

Teva has omitted the part of the April 1994 Data Table in which Dr. Pinchasi, in her own handwriting, wrote the April 1994 date on the top of the document and the words "Cop-1 Forum." (July Tr. 150:2-18.) Teva also omits that of the more than 2 million pages of information produced by Teva, this document was the only evidence admitted at trial showing the molecular weights and toxicity results for each of the batches of copolymer-1 listed in the patents-in-suit and that it was the only such document located in Mr. Nachshen's patent file. (DTX 999A.)[3]

581. Dr. Pinchasi testified that she may have considered the information in the April 1994 Data Table when she was gathering biological data on May 24, 1994, but she had no specific recollection of doing so. (July Tr. (Pinchasi) 125:2-7.)

[3] Teva has claimed that the April 1994 data table does not show the percentage of species above and below 40 kDa for the batches in the table of Example 2B and has suggested that Pinchasi and Nachshen may not have used the April 1994 data table to draft the patents-in-suit, despite Nachshen having two copies of it in his patent file. But Teva never produced a single document showing the "species" data for the examples in Example 2B.

Sandoz's Response:

The Court should reject that proposed finding and instead find that Dr. Pinchasi did consider the April 1994 data table on the evening of May 24, 1994. The Court should make these additional findings:

SDZ367. Two separate copies of the April 1994 Data Table appear in Mr. Nachshen's patent file. (DTX 999A at TEV001222355-RC, 417-RC.) Pinchasi was the only source of toxicity data. (July Tr. 155:8-19; 204:12-22.) [redacted] Sandoz has proven by clear and convincing evidence that Dr. Pinchasi relied upon the April 1994 Data Table to select data for Example 2 of the patent application.

(1) The April 1994 Data Table is Not Consistent with Example 2

582. Defendants assert that the April 1994 Data Table should have been disclosed to the PTO because, they argue, it is inconsistent with Example 2 of the patent.

Sandoz's Response:

Teva's statement is misleading and overly simplistic. The "April 1994 Data Table" is one example of toxicity data that was inconsistent with the toxicity data provided by Dr. Pinchasi to the PTO and was withheld from the PTO, but it is not the only example. Had Dr. Pinchasi disclosed that data, or any other complete picture of the toxicity data to the PTO, the PTO would not have allowed the claims of the patents-in-suit to issue.

583. Example 2 of the patents-in-suit discloses a correlation, or trend, between molecular weight and toxicity. (PTX 1, col. 4:12-27.) As molecular weight increases, toxicity, as shown by percent degranulation in the RBL test, increases. (July Tr. (Baird) 600:7-14.)

Sandoz's Response:

Teva misrepresents the record. Dr. Baird did not testify that the data in Example 2 described a "trend." She said nearly the opposite, namely that "one could not easily extrapolate what's happening between those -- those two ranges of molecular weight." (July Tr. 600:7-23 (Baird).) In the very next line of transcript, Teva's counsel tried to get Dr. Baird to say that there was a "trend" in Example 2, but she could not answer the question. (*Id.* at 600:24-601:3.) Dr. Baird continued:

> Q. In your opinion does the RBL degranulation data in the patent disclose that there is a clear difference between the low molecular weight copolymer-1 and the high molecular weight copolymer-1?
>
> A. Well, the data shows that, with the examples given, there is a -- there is a clear difference. What it doesn't say is what happens between the two different molecular weight -- pairs of molecular weight species.

(*Id.* at 601:5-12.) Rather than describing a trend, Dr. Baird says there is no information about what happens between the two extremes cited in the patent. Dr. Kimber's testimony was consistent with Dr. Baird's, as both experts agreed that the data provided in Example 2 suggests two "camps" with clear differences, and not merely a trend or probability of lower toxicity at lower molecular weights and vice versa. (July Tr. 401:7-15 (Kimber); July Tr. 601:5-12 (Baird).)

Both experts also agreed, based upon a review of a portion of Teva's toxicity data, that the toxicity data for other copolymer-1 batches not shown in the patent did not show a clear demarcation in toxicity above and below 9,000 daltons or any other molecular weight cutoff. (July Tr. at 601:13-24; 605:9-18 (Baird); 404:19-406:6 (Kimber).) In contrast, only the black and white picture presented in Example 2 was provided to the PTO. Teva characterized the difference in toxicity in Example 2 as distinct from the prior art and unexpected, not as merely a

"trend." (PTX 13 at TEV000304151-152; PTX 17 at TEV000304385; PTX 18 at TEV000310450-51; PTX 19 at TEV000304498.)

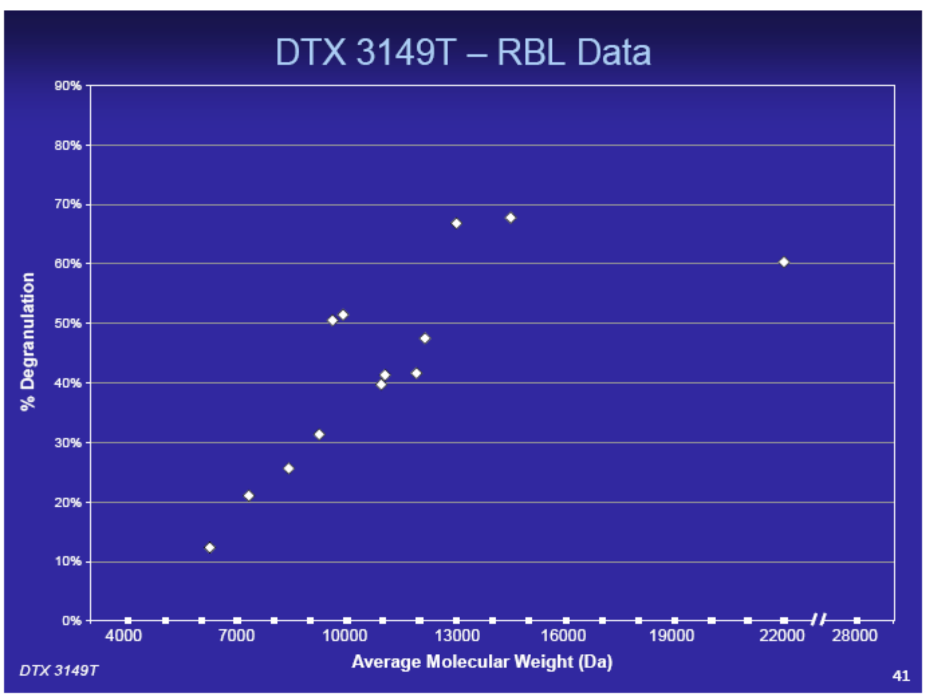
584. The evidence showed that the data in the April 1994 Data Table is consistent with the trend disclosed in Example 2 of the patents.

Sandoz's Response:

Again, Teva misrepresents the record. Neither of the expert witnesses testified that Example 2 of the patents discloses a trend. Dr. Kimber and Dr. Baird agreed that the data provided in Example 2 suggests two "camps" with clear differences, and not merely a trend or probability of lower toxicity at lower molecular weights and vice versa. (July Tr. 401:7-15 (Kimber); July Tr. 601:5-12 (Baird).)

585. Dr. Baird, a recognized expert in the RBL degranulation test, took the molecular weight and RBL degranulation data contained in the April 1994 Data Table and plotted them on the graph shown in Figure 26 below. She found that the data in the April 1994 Data Table show the same trend as seen in Example 2 -- increasing RBL degranulation with increasing molecular weight. (July Tr. (Baird) 603:7-604:5; PTX 887 at 40.)

Figure 26



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Sandoz's Response:

Teva misrepresents the record. Neither of the expert witnesses testified that Example 2 of the patents discloses a trend. Dr. Kimber and Dr. Baird agreed that the data provided in Example 2 suggests two "camps" with clear differences, and not merely a trend or probability of lower toxicity at lower molecular weights and vice versa. (July Tr. 401:7-15 (Kimber); July Tr. 601:5-12 (Baird).)

Both experts also testified that the toxicity data for other copolymer-1 batches not shown in the patent did not show a clear demarcation in toxicity above and below 9,000 daltons or at any other toxicity cutoff. (July Tr. at 601:13-24; 605:9-18 (Baird); 404:18-406:5 (Kimber).) In contrast, only the black and white picture presented in Example 2 was provided to the PTO. Teva characterized the difference in toxicity in Example 2 as distinct from the prior art and unexpected, not as merely a "trend." (PTX 13 at TEV000304151-152; PTX 17 at TEV000304385; PTX 18 at TEV000310450-51; PTX 19 at TEV000304498.)

Sandoz agrees that Dr. Baird testified that when plotted, the data from the "April 1994 Data Table" show "that lower molecular weight species stimulate less degranulation than higher molecular weight species in a consistent trend." (July Tr. 603:25-604:5.)

586. Dr. Pinchasi likewise testified that the data in the April 1994 Data Table "very clearly and strongly supports the correlation we have discussed – the higher the average molecular weight, the higher percentage of RBL release." (July Tr. (Pinchasi) 125:14-19.)

Sandoz's Response:

Dr. Pinchasi's testimony refers to her perceived "trend" or "probability" of lower toxicity at lower molecular weights, which she admits were nowhere in the patent application. (July Tr. at 262:12-264:7.)

587. Even Defendants' expert Dr. Kimber conceded that the RBL data in the April 1994 Data Table, like all of the other data he has seen in this case, reflect a trend of increasing RBL degranulation with increasing average molecular weight. (July Tr. (Kimber) 446:22-

447:15, 465:2-3, 466:10-19.)

Sandoz's Response:

Dr. Kimber did not testify that Example 2 of the patents discloses a trend. Dr. Kimber and Dr. Baird agreed that the data provided in Example 2 suggests two "camps" with clear differences, and not merely a trend or probability of lower toxicity at lower molecular weights and vice versa. (July Tr. 401:7-15 (Kimber); July Tr. 601:5-12 (Baird).)

Dr. Kimber testified that the data in the April 1994 Data Table is inconsistent with the data in the patent. (July Tr. 408:12-409:7; 465:2-3). He agreed that the data in the April 1994 Data Table "by and large [show] that the likelihood of higher release was associated with higher average molecular weights. But there are those important caveats in identifying that trend." (July Tr. 466:10-19.) Those caveats include that the data do not show replicates or standard deviations. (July Tr. 446:25-447:15.)

Both experts also testified that the toxicity data for other copolymer-1 batches not shown in the patent did not show a clear demarcation in toxicity above and below 9,000 daltons. (July Tr. at 601:13-24; 605:9-18 (Baird); 404:19-406:6 (Kimber).) In contrast, only the black and white picture presented in Example 2 was provided to the PTO. Teva characterized the difference in toxicity in Example 2 as distinct from the prior art and unexpected, not as merely a "trend." (PTX 13 at TEV000304151-152; PTX 17 at TEV000304385; PTX 18 at TEV000310450-51; PTX 19 at TEV000304498.)

(2) Example 2 is Not Representative of Teva's Toxicity Data as a Whole

588. The Weizmann and Teva scientists performed hundreds of RBL degranulation tests on batches of copolymer-1 during development of the product. (July Tr. (Arnon) 332:8-334:2; *see, e.g.*, PTX 34T; PTX 36T; PTX 53T; PTX 54.) The April 1994 Data Table contains only a small fraction of those test results.

Sandoz's Response:

Sandoz disputes this to the extent it suggests that the data within PTX 34T; PTX 36T; PTX 53T; PTX 54 is exhaustive. It excludes RBL data from at least DTX 999A, DTX 3059, DTX 3149, DTX 3477, DTX 3317, DTX 1259, PTX 43T, and DTX 1262. Dr. Pinchasi and Dr. Arnon testified that the RBL testing was performed by Weizmann scientists, not Teva scientists. (July Tr. 332:8-334:2 (Arnon); 30:9-13; 90:23-91:2; 126:13-16; 173:7-24 (Pinchasi).)

589. The evidence showed that the data in Example 2 of the specification was a fair and accurate representation of the data generated by the Teva and Weizmann scientists as a whole. (July Tr. (Arnon) 332:8-334:2; July Tr. (Pinchasi) 30:14-20, 80:13-81:13; July Tr. (Baird) 601:13-24; PTX 887 at 44.)

Sandoz's Response:

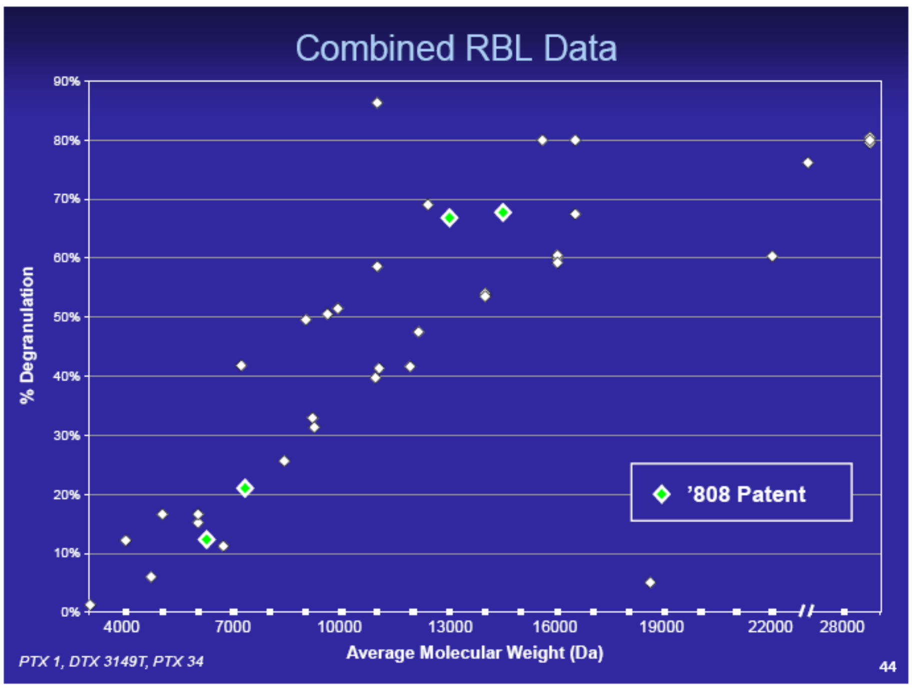
Dr. Pinchasi testified that she knew of many individual data points that are inconsistent with the data in the patent application. (July Tr. at 245:17–246:4.) She testified that a number of batches with molecular weights of around 6,250 and 7,300 daltons were toxic using the RBL test. (DTX 3059; PTX 43T; July Tr. at 238:2-239:11, 244:7-245:11, 245:17-246:4.) She also testified that batches having molecular weights around 13,000 and 14,500 were non-toxic using the RBL test. (DTX 3477; July Tr. at 253:12–255:4.) This inconsistent data was not shown in the patents.

Despite knowing of the large amounts of data available, Teva only included toxicity data for the four batches of copolymer-1 in the patent application. (July Tr. at 207:10-14.) Dr. Kimber testified that a person of skill in the art would have understood from the description of four copolymer-1 batches in the RBL testing section of the patents that only four batches were tested, and would not have understood that Teva had data for many more batches from the same body of evidence. (July Tr. at 401:16 – 402:3.)

Dr. Baird did not testify that Example 2 of the specification was a fair and accurate representation of the data as a whole. She said nearly the opposite, namely that "one could not easily extrapolate what's happening between those -- those two ranges of molecular weight." (July Tr. 600:7-23; 601:5-12 (Baird).) Rather than describing the representativeness of the data, Dr. Baird says there is no information about what happens between the two extremes cited in the patent. The absence of data in this intervening molecular weight range cannot be said to be a "fair and accurate" representation of data.

590. Dr. Baird took molecular weight and RBL degranulation data for several different batches of copolymer-1 found in Teva's internal files for several different batches of copolymer-1 that had been cited by Defendants' experts and added them to the graph she had created for the data in the April 1994 Data Table.

Figure 27



591. She again found that the data showed "a very clear trend" consistent with the trend shown in Example 2. (July Tr. (Baird) 601:13-24, 605:14-18; PTX 887 at 44.)

Sandoz's Response:

Dr. Baird did not testify that Example 2 of the patents discloses a trend. Dr. Kimber and Dr. Baird agreed that the data provided in Example 2 suggests two "camps" with clear differences, and not merely a trend or probability of lower toxicity at lower molecular weights and vice versa. (July Tr. 401:7-15 (Kimber); July Tr. 601:5-12 (Baird).) Dr. Baird's figure is a selection of the RBL data admitted at trial; it leaves out data from at least DTX 999A, DTX 3059, DTX 3149, DTX 3477, the first two pages of DTX 3317, DTX 1259, PTX 43T, and DTX 1262. The figure likewise does not show the 30% cut-off emphasized by Dr. Pinchasi. (July Tr. at 58:8-13; 75:15-17; 180:10-13.) At the 30% degranulation level emphasized by Dr. Pinchasi, only 25% of the batches having a molecular weight of 7,000 to 10,000 daltons are "non-toxic." (Batches 123090 and 123095 from DTX 3149T.) This low probability of being "non-toxic" under the RBL test is not found anywhere in the patents.

Sandoz agrees that Dr. Baird testified that when plotted, these data show "very consistent trend that lower molecular weight species stimulate less degranulation than higher molecular weight species." (July Tr. 605:16-18.)

592. Teva and Weizmann's *in vivo* toxicity data is similarly consistent with Example 2, and Defendants provided no expert testimony to the contrary. Although the only copolymer-1 batch in the April 1994 Data Table that failed the *in vivo* toxicity test had a molecular weight of 22,000 daltons, Teva and Weizmann had internal data on many batches of copolymer-1 with molecular weights between 10,000 and 22,000 daltons that had failed that test. (July Tr. (Pinchasi) 126:4-8; *see, e.g.*, PTX 34-T.)

Sandoz's Response:

Neither Plaintiffs nor Defendants provided expert testimony on the issue of whether Teva and Weizmann's in vivo toxicity data is consistent with Example 2. Nor did Plaintiffs provide expert testimony on whether Teva and Weizmann's in vivo toxicity data shows a clear demarcation in toxicity above and below 9,000 daltons. The Court should make these findings:

SDZ368. The patents contain only three mouse death data points provided in Example 2 of the patents. (PTX 1, 808 patent, col. 3:23-45.) The patent *in vivo* toxicity data is not consistent with the April 1994 Data Table. The patent shows that molecular weights of 7,300 and 8,400 daltons produced no mouse deaths, while 22,000 daltons, in the range of the prior art, produced three mouse deaths. (*Id.*) Teva and Dr. Pinchasi knew that the 13,000 and 14,500 dalton batches, represented as part of the RBL data in Example 2, produced no mouse deaths, and this data was not disclosed to the PTO. (DTX 3149; July Tr. at 149:16-150:21 (Pinchasi).) Teva and Dr. Pinchasi also knew that copolymer-1 batches with molecular weights of 9,900, 10,950, 11,050, 11,900, and 12,150 daltons produced no mouse deaths. (*Id.*) Toxicity data for these batches were also kept from the PTO.

593. Defendants did not provide their expert Dr. Kimber with all of the RBL degranulation and *in vivo* mouse test data that had been produced by Teva in this case. (July Tr. (Kimber) 426:21-429:16, 438:13-439:1.) Accordingly, Dr. Kimber did not know whether the data in the April 1994 Data Table reflected the universe of toxicity data that had been generated by Weizmann and Teva, and could not provide an opinion on whether Teva's data as a whole was consistent with Example 2. (July Tr. (Kimber) 438:18-439:5.)

Sandoz's Response:

Sandoz sought to present the entire toxicity data to the Court at trial. Throughout the trial, Teva consistently objected to the admission of its own toxicity data. (*E.g.*, July Tr. 231:11-15; 247:20 - 251:23.) The Court consistently overruled those objections. (*E.g.*, July Tr. 233:16-19; 251:24-25.)

The Defendants provided Dr. Kimber all of the RBL data that could be recognized as such from Teva's over two million page document production, much of which was handwritten and in Hebrew. Dr. Kimber was provided all of the documents supporting the information that went into the patent. Sandoz incorporates Mylan's response to this paragraph regarding the

Defendants' efforts to force Teva to produce and identify toxicity data in a meaningful way. Regardless whether Dr. Kimber saw every single RBL test ever run at Teva, he had adequate data to form his opinions, which were not contradicted by any Teva witness, namely that Teva's data does not show a clear toxic/non-toxic molecular weight value that would establish a patentably distinct "critical range."

Teva limited Dr. Baird's review of Teva data to exactly what was reviewed by Dr. Kimber. (July Tr. 625:18-25.) If Teva knew that Dr. Kimber had missed some of the toxicity data, and if that data supported Teva's theory of the case, surely it would have given the data to Dr. Baird to present at trial in support of Teva's positions.

Teva also mischaracterizes Dr. Kimber's testimony. Dr. Kimber primarily was the Defendants' *in vitro* RBL expert. Dr. Rice primarily served as the *in vivo* mouse expert. Dr. Kimber testified that he did not know whether he saw all of the *in vivo* mouse data, and that he did not know whether the mouse data in the April 1994 Data Table was reflective of Teva's *in vivo* mouse data. (July Tr. 438:18-439:5.) This portion of his testimony was limited to the mouse data, and did not implicate his knowledge of the RBL test.

(3) <u>The Patent Office Was Not Aware That Not All High Molecular Weight Copolymer-1 Batches Were Toxic</u>

594. Plaintiffs assert that Teva represented to the PTO in Example 2 that all batches of copolymer-1 above 10,000 daltons were toxic, and that the April 1994 Data Table shows otherwise. This is also incorrect.

<u>*Sandoz's Response:*</u>

This proposed finding has no citation and refers to Teva disagreeing with "Plaintiffs." The Court should not adopt any findings unsupported by citation to credible evidence of record.

595. As Dr. Baird testified, Example 2 describes a trend showing increasing toxicity with increasing molecular weight. (July Tr. (Baird) 600:7-23.) It does not state or imply that all batches above 10,000 daltons were toxic and all batches below were not. (July Tr. (Baird) 600:7-23.)

Sandoz's Response:

Teva misrepresents the record. Dr. Baird did not testify that the data in Example 2 described a "trend." She said nearly the opposite, namely that "one could not easily extrapolate what's happening between those -- those two ranges of molecular weight." (July Tr. 600:7-23 (Baird).) In the very next line of transcript, Teva's counsel tried to get Dr. Baird to say that there was a "trend" in Example 2, but she could not answer the question. (*Id.* at 600:24-601:3.) Dr. Baird continued:

> Q. In your opinion does the RBL degranulation data in the patent disclose that there is a clear difference between the low molecular weight copolymer-1 and the high molecular weight copolymer-1?
>
> A. Well, the data shows that, with the examples given, there is a -- there is a clear difference. What it doesn't say is what happens between the two different molecular weight -- pairs of molecular weight species.

(*Id.* at 601:5-12.) Rather than describing a trend, Dr. Baird says there is no information about what happens between the two extremes cited in the patent.

596. In fact, Example 2 explicitly concludes that "[a]s can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin indicative of toxicity is low, and vice versa." (PTX 1, col. 4:25-27.) As Dr. Baird explained, this statement indicates a trend in the data, not any hard cut-off. (July Tr. (Baird) 600:7-14.)

Sandoz's Response:

Sandoz strongly encourages the Court to scrutinize Teva's description of Dr. Baird's testimony. Dr. Baird says no such thing. When talking about the *data in Example 2*, she never describes a "trend" in the data. Later, when talking about Teva's *internal data* not disclosed to the PTO, Dr. Baird says that the withheld data shows a "trend." (July Tr. 601:17-24.)

597. Momenta's own scientists outside the context of this litigation understood that the data in Example 2 showed a trend. An internal report discussing the patents-in-suit states that the Momenta scientists found that "the higher the Average Molecular Weight, the greater the percent serotonin released." (PTX 186 at MMT00950946.)

Sandoz's Response:

Momenta documents from 2007 have no bearing on whether Teva committed inequitable conduct in 1994. Regardless, the document cited by Teva to support what "Momenta's own scientists understood" is a "draft technical report" that was never finalized. (PTX 882 at 97:3-19.) The above quote is in a two-paragraph section entitled "Background," which cites to four total references. (PTX 186 at MMT00950946.) The Court should reject Teva's proposed finding that Momenta scientists "understood that the data in Example 2 showed a trend" when even Teva's own expert did not reach that conclusion.

598. Moreover, Dr. Bornstein's 1987 article, cited in the specifications of the patents-in-suit, explicitly states that some batches of copolymer-1 having a molecular weight of between 14,000 and 23,000 daltons showed less than 30% degranulation in the RBL assay, *i.e.*, were "non-toxic." (PTX 1, col. 1:25-28; PTX 11 at TEV000309437; PTX 31 at 408-09.) The file histories indicate that the PTO examiner reviewed and considered the Bornstein article during the prosecution of the patents-in-suit. (PTX 18 (File History of U.S. Patent 6,362,161 ("'161 File History")) at TEV000310385-389; PTX 14 (File History of U.S. Patent No. 5,981,589 ("'589 File History")) at TEV000309018-21; PTX 21 (File History of U.S. Patent No. 7,199,098 ("'098 File History")) at TEV000308838-842.)

Sandoz's Response:

As discussed in Sandoz's opening post trial brief, Teva told the FDA and the PTO different stories about the 1987 Bornstein article. [redacted] To the PTO, Teva presented just the Bornstein paper, which stated that the molecular weight of the same copolymer-1 had a molecular weight from 14,000 to 23,000 daltons. (PTX 31 at 408.) To the extent that the PTO considered the 1987

Bornstein article, the PTO did not have the benefit of what Teva was telling the FDA. Instead, the PTO presumably considered the Bornstein paper to be describing a copolymer-1 composition with an unspecified molecular weight of 14 to 23 kDa. (PTX 31 at 408.)

While the 1987 Bornstein article (PTX 31) is cited in the Background of the Invention section of the patents-in-suit, Teva did not include the Bornstein article in any of its Information Disclosure statements until April 30, 2004, ten years after filing the original application. (PTX 20 at TEV000304847.) Teva provides the Court three citations for the proposition that "the PTO examiner reviewed and considered the Bornstein article during the prosecution of the patents-in-suit." None of the three cites contains the 1987 Bornstein paper (PTX 31). One of the three cites is to an August 18, 1998 Information Disclosure Statement (PTX 14 at TEV000309014-021), which falsely suggests that the PTO received and considered the 1987 Bornstein paper before issuing the first of the nine patents-in-suit on September 1, 1998. (PTX 1.) In fact, seven of the nine patents-in-suit issued before Teva listed the 1987 Bornstein paper in an Information Disclosure Statement and provided a copy to the PTO. (PTX 1-7.)

599. Thus, the PTO was well aware from both the specification and prosecution of the patents that not all higher molecular weight copolymer-1 batches were toxic. Any such information in the April 1994 Data Table would have been cumulative.

Sandoz's Response:

This attorney argument makes little sense and should not be adopted by the Court. The omitted information, both in the April 1994 Data Table and elsewhere within Teva, shows that Teva's claimed molecular weight ranges were not "critical" to a showing of improved toxicity. Teva gave the PTO the impression that it had discovered such a "critical" range. Because Teva's primary barrier to patentability was the 10 kDa cutoff of the '550 patent, and because Teva claims it is entitled to patent protection just below the molecular weight range cutoff of the '550 patent, the "unexpected results" inquiry must examine the range where Teva's patent scope ends

and the ’550 prior art scope begins, i.e., around 10 kDa. The Bornstein paper, as far as was known to the PTO, did not provide answers regarding molecular weights around 10 kDa because the PTO, at best, was under the impression that the Bornstein paper described copolymer-1 with a minimum average molecular weight of 14 kDa. The April 1994 Data table included more relevant information, including seven additional data points between 8.4 kDa and 13 kDa that were not apparent from the face of the 1987 Bornstein paper. Thus, they could not be cumulative of Bornstein.

(iv) Dr. Pinchasi’s Views on the RBL Degranulation Test Were Material

(1) Dr. Pinchasi Did Not Believe the RBL Degranulation Test To be a Reliable Screening Test for Toxicity

600. In a December 1989 memo, Dr. Pinchasi set forth her rationale for adopting a second screening test, the *in vivo* toxicity test, in addition to the RBL degranulation test. (DTX 3385.) Defendants point to this memo as evidence that Dr. Pinchasi believed that the RBL test could not be used as a toxicity screen. That conclusion cannot be drawn.

Sandoz’s Response:

Trial Exhibit DTX 3385 is actually two different documents pulled from Neil Nachshen’s patent file, as can be seen by comparing the Bates numbers.[4] The First document, entitled “In-Vivo Safety Assay,” is four pages. (DTX 3385 at TEV001222388-391; DTX 999A at TEV001222388RC-391RC.) The second document is entitled “Safety Assays,” and is five pages. (DTX 3385 at TEV001222392-396; DTX 999A at TEV001222392RC-396RC.) The person responsible for the “In-Vivo Safety Assay” document was Dr. Teitelbaum, not Dr. Pinchasi. (DTX 3385 at TEV001222388; DTX 999A at TEV001222388RC.) Dr. Pinchasi later approved the document as evidence by her signature in the “Approved” box at the top of the page. (*Id.*) While the consecutive page numbering on the document from 361-368 shows that

[4] The “RC” at the end of the Bates numbers in DTX 999A merely indicates that it is a revised, color print of the document.

the documents were side-by-side when compiled and submitted to the FDA (compare number on DTX 1146 FDA submission), the two documents together are not a single "December 1989 memo" whereby "Dr. Pinchasi set forth her rationale for adopting a second screening test." Sandoz relied on the "Safety Assays," document as evidence that Dr. Pinchasi withheld from the PTO Teva's doubts about the RBL test.

601. As Dr. Pinchasi explained, she believed that the RBL degranulation test was "very good" for screening toxic batches during process development, but that she "didn't think it was sufficiently reproducible to [serve] as a sole, as a single, an only methodology to be used to decide whether a batch is safe for clinical use or not." (July Tr. (Pinchasi) 102:24-103:17.)

Sandoz's Response:

Sandoz does not dispute that when questioned by her lawyers, Dr. Pinchasi reinterpreted the statements in the actual document. However, on cross examination, Dr. Pinchasi admitted that:

- "the RBL system is not sufficiently reproducible so as to afford the ultimate analysis for the safety of our batches"
- "the upper permitted level of RBL degranulation (40%) was established by the Weizmann researchers arbitrarily"
- "the RBL system is inconsistent in its reproducibility, and both inter-assay and intra-assay large variations were observed"
- "We thus feel that this assay can not be properly controlled."

(DTX 3385 at TEV001222392-94; DTX 999A at TEV001222392RC-94RC; July Tr. 161:5-165:6, 207:15-208:23 (Pinchasi).)

602. Teva decided to use both the RBL degranulation test and the in vivo toxicity test because they viewed them as complementary in terms of how they can be used to predict clinical safety. (July Tr. (Pinchasi) 29:1-19, 103:9-20.)

Sandoz's Response:

Sandoz does not dispute that at trial, Dr. Pinchasi offered a new interpretation of her written words from 1989. For example, in 1989, she said that the RBL assay was "very

convenient" for screening many batches at a time. (DTX 999A at TEV001222392-RC.) At trial, she interpreted that to mean "very good." (July Tr. (Pinchasi) 29:1-19, 103:9-20.) The Court must assess Dr. Pinchasi's credibility in terms of what she wrote in 1989, what she told the PTO in 1994, and what she said at trial in 2011.

603. The Court credits Dr. Pinchasi's testimony that, despite some concerns about using the RBL degranulation test as the only test for clinical use, she and others at Teva continued to use that test to draw conclusions about the toxicity of batches of copolymer-1. (July Tr. (Pinchasi) 102:24-104:1, 104:16-20.)

Sandoz's Response:

Dr. Pinchasi's testimony on this issue was not credible. She testified that Teva continued to use the RBL test "for several good years" after the 1989 memo. Teva's 2 million plus page production had no evidence that Teva was using the RBL test the night that Pinchasi told the PTO that the RBL test was "characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system." (PTX 1, '808 patent, col. 3:50-53.)

604. Dr. Pinchasi's testimony is corroborated by internal Teva documents showing that Teva continued to use the RBL degranulation assay in conjunction with the *in vivo* toxicity test for many years after Dr. Pinchasi's December 1989 memo was written. (July Tr. (Pinchasi) 101, 103:18-104:15; PTX 723.)

Sandoz's Response:

By "many years after Dr. Pinchasi's December 1989 memo," Teva means, at best, three years. Teva's only evidence of continued use of the RBL test after expressing reservations in 1989 about the assay is PTX 723, a December 1990 product profile for copolymer-1, and PTX 62, a 1992 chart showing some RBL testing that took place at some unknown time before the chart was compiled. If Teva had a document showing that RBL was used later than 1992, it surely would have produced it and provided it at trial. Instead, Teva asks the Court to make a finding of fact that the RBL test was used "for many years" after December 1989. The Court should reject that proposed finding.

Even if Teva used the RBL test through 1992, the relevant inquiry is what Dr. Pinchasi knew in her head when making representations to the PTO in May 1994. There is absolutely no evidence that Teva was still using the RBL test in 1994 when Pinchasi made her representations to the PTO.

605. For example, a December 1990 FDA submission contains data on both RBL degranulation testing and *in vivo* toxicity testing performed on the same batches in May 1990. At that time, the RBL degranulation test was being used routinely by Teva and the Weizmann Institute to screen batches of copolymer-1. (July Tr. (Pinchasi) 95:21-97:9, 101; 103:18-104:15; PTX 723 at TEV000599237, 241, 245, 249, 253, 257, 260.)

Sandoz's Response:

The relevant inquiry is what Dr. Pinchasi believed when making her representations to the PTO in 1994.

606. The RBL degranulation test was still being used by the Weizmann Institute and Teva at least through December 1992. (July Tr. (Pinchasi) 99:5-100:3; PTX 62.)

Sandoz's Response:

Sandoz admits that Teva produced a 1992 document that charts some RBL testing that was done in 1992 or earlier. But the Court should find that Teva had stopped using the RBL degranulation test by the time Dr. Pinchasi made her representations to the PTO on May 24, 1994, because there is no evidence that the RBL test was used after 1992.

(2) Professor Arnon's Views Are Mistated and Do Not Overcome Dr. Pinchasi's Inequitable Conduct

607. The RBL degranulation test was not selected by Dr. Pinchasi. Inventor Professor Arnon selected the test after concluding that it was an appropriate assay for screening batches of copolymer-1 for toxicity. Even after Teva took on development of copolymer-1, the RBL testing continued to be performed at the Weizmann Institute. (July Tr. (Pinchasi) 30:7-20; July Tr. (Arnon) 332:8-25; July Tr. (Baird) 608:25-609:10.)

Sandoz's Response:

Sandoz agrees that Dr. Pinchasi did not select the RBL test. Rather, Dr. Pinchasi discovered that it was not a reproducible or controllable test, but went ahead and represented to

the PTO that the test could be "used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (PTX 1, '808 patent, col. 3:49-68.) Dr. Arnon had been working on copolymer-1 since approximately 1966. (July Tr. 309:8-311:8.) Dr. Arnon had no involvement in the preparation of the patent application on the evening of May 24, 1994. (*See* Teva FOF ¶ 570.)

608. Before making the decision to adopt the RBL degranulation test, Professor Arnon personally read all the literature about the test, including articles by Dr. Reuben Siraganian's group at NIH, who were the leading experts on the test. (July Tr. (Arnon) 321:19-25.)

Sandoz's Response:

Dr. Arnon's decision to use the RBL test based on her reading of the 1981 Siraganian paper is irrelevant. (PTX 522; July Tr. 322:21-323:4.) Dr. Pinchasi later discovered that it was not a reproducible test as used by Teva for copolymer-1, but withheld that information from the PTO in 1994. Dr. Arnon was not a named inventor of the patents-in-suit when the inequitable conduct occurred.

609. One of the literature references that Professor Arnon considered was a 1981 article ("the Barsumian article") by Dr. Barsumian, who was a member of the Siraganian group at NIH. The Barsumian article reported that the RBL degranulation test had a reproducibility of approximately 20%. (July Tr. (Arnon) 325:14-326:1; PTX 522 at 320.) Given this data, Dr. Barsumian concluded that the test was "quite reproducible." (July Tr. (Arnon) 321:19-326:13, 337:7-16; PTX 522 at 322.)

Sandoz's Response:

Dr. Barsumian was not using the RBL test with copolymer-1. Dr. Pinchasi admitted at trial that she discovered by 1989 that the test was not reproducible for use with copolymer-1. The relevant inquiry is whether she was required to disclose her experience applying the RBL test to copolymer-1, or whether she was permitted to pretend that it was a reproducible and reliable test.

610. Based on the literature available at the time and Professor Arnon's experience with biological assays, she and her colleagues at the Weizmann Institute determined that the

RBL degranulation test, with its approximately 20% reproducibility, was "quite reliable." (July Tr. (Arnon) 321:8-326:25, 336:2-337:17; PTX 522; PTX 711; DTX 3114.)

Sandoz's Response:

This is irrelevant for the reasons stated above.

611. Weizmann and Teva's protocol for performing the RBL degranulation test was contained in a specification that had been drafted, not by Dr. Pinchasi, but by Weizmann scientist Dr. Teitelbaum. Professor Arnon reviewed the RBL specification. (July Tr. (Pinchasi) 89:23-91:4; July Tr. (Arnon) 334:14-23; DTX 3114.) The RBL specification was later signed and approved by Dr. Pinchasi. (July Tr. (Pinchasi) 89:23-91:4; DTX 3114.)

Sandoz's Response:

Teva's proposed findings are confusing and should not be adopted because they do not differentiate between two RBL memos in the record, one of which is entitled "RBL – Degranulation Test Method G2" (DTX 3114; DTX 999A at TEV001222397RC-403RC), and the December 1989 Memo entitled "Safety Assays" (DTX 999A at TEV001222392RC-396RC).

The "protocol for performing the RBL degranulation test" referred to by Teva in its proposed finding refers to the "RBL – Degranulation Test Method G2" protocol, which served as the text for Example 2B in the patents-in-suit. (Compare PTX 1, '808 patent, Example 2B to DTX 3114 at TEV000811362.) Teva omits the significant fact that "RBL – Degranulation Test Method G2" is from before Dr. Pinchasi discovered in 1989 that there were significant problems with the RBL assay. The protocol is found three places in the record. First, it is in Neil Nachshen's patent file. (DTX 999A at TEV001222397RC-403RC.)[5] Second, the protocol was introduced as a stand-alone document when Teva's counsel showed it to Dr. Pinchasi, and she claimed that she did not know the date of the document. (July Tr. 89:23-91:11; DTX 3114.) Finally, over many objections by Teva, Sandoz later proved that the document was included in a 1988 FDA submission. (DTX 1146 at TEV000881293-294 (showing the 1988 date),

[5] The first page of the protocol is missing from Nachshen's notebook because it was pasted into the original patent application. (DTX 11 at TEV000309442.)

TEV000881362-370; July Tr. at 387:9-391:6).) Sandoz has shown by clear and convincing evidence that the RBL protocol that was used in Example 2B in the patents-in-suit predated Dr. Pinchasi's 1989 memo expressing doubts about the RBL assay.

612. According to the RBL specification drafted by Dr. Teitelbaum, the RBL degranulation test was used "to screen out those batches of cop-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (DTX 3114 at TEV000881362.) As Professor Arnon testified, she still believes today that this is an accurate statement of the appropriate use of the RBL degranulation test. (July Tr. (Arnon) 334:24-335:14.)

Sandoz's Response:

This is largely irrelevant because it has no bearing on Dr. Pinchasi's intent to deceive the PTO in 1994. Regardless, Teva is mischaracterizing Dr. Arnon's testimony. Dr. Arnon testified about the past use of the RBL test in the testimony cited by Teva. She merely agreed that sitting here today, she still believes that the statement from the pre-1989 protocol was accurate – that the RBL test was used in order to screen out batches of copolymer-1 which evoke substantial degranulation. She did not testify that it is appropriate today to use the RBL test.

613. The RBL specification shows that the test was validated, meaning that it was proven to be precise and reproducible enough for the purposes for which it was being used. (July Tr. (Pinchasi) 92:22-93:17; DTX 3114 at TEV000881368.) The precision of the RBL degranulation test (in terms of its relative standard deviation ("RSD")) was reported as ± 19%, and its reproducibility (in terms of RSD) was reported as ± 26%. (July Tr. (Pinchasi) 94:9-15; DTX 3114 at TEV000881368-369.) Professor Arnon testified that this level of precision and reproducibility was both acceptable and within the range of what the Weizmann scientists expected. (July Tr. (Arnon) 336:2-337:6.)

Sandoz's Response:

This is all irrelevant because it predates Dr. Pinchasi's 1989 memo and Teva's subsequent abandonment of the RBL test. Teva told the PTO only about the 1988 protocol without telling the PTO that in 1989, it discovered that the test was not reproducible or controllable and Teva was no longer using the test in 1994.

(3) The RBL Degranulation Test Was Not Well Accepted Within Teva.

614. Dr. Baird testified at trial that the RBL degranulation test is a very reliable and reproducible test that is widely used by the scientific community as a model for immediate hypersensitivity that might occur in humans. (July Tr. (Baird) 585:9-21, 595:4-16, 596:25-597:8, 610:6-20, 611:15-22; PTX 522.)

Sandoz's Response:

Sandoz is not taking the position that the RBL test is not useful for any purpose. Rather, when used by Teva as a toxicity test with copolymer-1, it had major flaws, which were appreciated within Teva by 1989, but not disclosed to the PTO.

615. Dr. Baird specifically testified that she agreed with the description of the RBL test set out in the patent, and believes it was reasonable for the Weizmann Institute and Teva scientists to use the test for the purpose described in the patent -- to "screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (July Tr. (Baird) 593:21-597:8.)

Sandoz's Response:

Sandoz does not contend that it was unreasonable to try the RBL test with copolymer-1. Teva did that. Eventually, it found that the test was not reproducible or controllable when used with copolymer-1. It stopped using it. It did not tell the PTO. That is the relevant inquiry.

616. This language in the patent was taken directly from the RBL specification written by the scientists at the Weizmann Institute. (July Tr. (Pinchasi) 286:11-288:16; PTX 1, col. 3:63-67; PTX 10 at TEV003009934; DTX 3114 at TEV000811362.)

Sandoz's Response:

Sandoz agrees that the text in Example 2B was taken from the 1988 RBL protocol, which predated Pinchasi's finding in 1989 that the RBL test was flawed as used by Teva for copolymer-1.

617. In fact, Defendants themselves have performed RBL degranulation testing and have acknowledged its acceptance in the scientific community.

Sandoz's Response:

This is misleading. Momenta did not use the RBL degranulation to test toxicity of glatiramer acetate. Rather, it used the RBL test to prove the sameness of its proposed glatiramer acetate product to Teva's Copaxone. (PTX 882 (Kishimoto Depo.) at 45:11-46:16.) There is no evidence in the record that RBL degranulation testing for the purpose of screening toxic batches of copolymer-1 is currently practiced in the scientific community.

618. Dr. Bhujanga Rao, defendant Natco's President of Research and Development, testified that Natco performed RBL degranulation testing, and that the RBL degranulation test is a "well-known toxicity test for hypersensitivity reactions to products" that is "predictive of hypersensitivity in humans." (PTX 883 (Rao Dep.) at 149:22-150:4.)

Sandoz's Response:

Sandoz takes no position regarding a deposition for which it was not noticed and did not attend other than to say that nothing a Natco witness stated in 2011 has any bearing on whether Dr. Pinchasi committed inequitable conduct in Israel in 1994. Sandoz incorporates Mylan's response to this proposed finding of fact.

619. [redacted]

Sandoz's Response:

What Momenta did in 2009 is irrelevant to whether Dr. Pinchasi committed inequitable conduct in 1994. Momenta's "similar" RBL test was done for a completely different reason. Momenta tested RBL degranulation in commercially available Copaxone. Then, it tested it in its proposed glatiramer acetate product. It compared the two results. (PTX 349 at SDZ00018127-132.) Momenta reported to the FDA that "based on this [RBL] measure of bioactivity Glatiramer Acetate Injection [Sandoz's proposed product] is equivalent to the RLD

[commercially available Copaxone].” (*Id.* at SDZ00018132.) This has nothing to do with the RBL test being used as a toxicity screen.

620. Although Defendants’ expert Dr. Kimber testified that the RBL degranulation test is not sufficiently reproducible to draw any conclusions about the toxicity of copolymer-1, he has limited experience with the test, and has never performed that test himself. (July Tr. (Kimber) 426:1-3, 426:8-17.) His testimony was based entirely on the variability for the test described in the RBL specification. [redacted]

<u>*Sandoz’s Response:*</u>

This is irrelevant and misleading. [redacted] None of this changes the fact that Dr. Pinchasi found the RBL test not to be reproducible for the very reason she told the PTO it was reproducible – “to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects.” (PTX 1, ’808 patent, col. 3:63-67.)

621. The fact that the Bornstein article, which appeared in the *New England Journal of Medicine* and was peer-reviewed, explicitly describes the use of the RBL degranulation test as a toxicity screen for copolymer-1 batches is further evidence that use of the test would have been generally accepted by the scientific community. (July Tr. (Arnon) 329:3-331:4; PTX 31 at 409.)

<u>*Sandoz’s Response:*</u>

The Bornstein paper, like the Teva protocol, predates Dr. Pinchasi’s discovery in her 1989 memo that the RBL test was not reproducible. She withheld that later-obtained belief in 1994. Giving the PTO even more information about the RBL test beyond what was in Example 2B should have given Dr. Pinchasi even more incentive to tell the PTO that her prior beliefs about the RBL test were wrong.

(4) <u>The Patent Office Was Not Told About the Lack of Reproducibility of the RBL Degranulation Test.</u>

622. Example 2 of the patents-in-suit cites to the same two literature references cited in the RBL specification–the Barsumian and Siraganian articles. The Barsumian article specifically

reported a reproducibility of ± 20% for the RBL degranulation test. (PTX 1, col. 3:50-55; PTX 522.) Thus, the Examiner was aware of the reproducibility of the test when making the decision to allow the claims to issue.

Sandoz's Response:

Sandoz agrees with Teva that the Examiner was left with the impression that the RBL tests were reproducible based on the Example 2 provided by Dr. Pinchasi. That is why Dr. Pinchasi's withholding of her knowledge that it was not reproducible amounts to inequitable conduct. If Pinchasi had been forthcoming, the Examiner would not have accepted the data in Example 2.

(v) Dr. Pinchasi's Intent to Deceive

(1) Dr. Pinchasi's Lacked Credibility

623. Dr. Pinchasi testified directly that she had no intention of deceiving the PTO when she supplied the biological data for the '037 patent application. (July Tr. (Pinchasi) 135:6-22.)

Sandoz's Response:

Sandoz does not dispute that Dr. Pinchasi testified in 2011 that she did not have intent to deceive. But a bare denial from the accused wrongdoer by itself cannot defeat a finding that she acted with an intent to deceive the PTO. *See, e.g.*, *GFI, Inc. v. Franklin Corp.*, 265 F.3d 1268, 1275 (Fed. Cir. 2001).

624. As she explained, when she reviewed the '037 application, she believed that the *in vivo* data reported in Example 2A was representative of the accumulated Weizmann data she was aware of at that time. She also believed that there was a correlation between *in vivo* toxicity measured by the test set forth in Example 2 and the molecular weight of copolymer-1 as set forth in Example 2. (July Tr. (Pinchasi) 129:14-130:1, 135:6-22.)

Sandoz's Response:

Example 2A is the in vivo mouse data. The testimony is not credible because as the head of the Copaxone project and as the person at Teva most knowledgeable about Teva's toxicity testing, Dr. Pinchasi had no factual basis to actually believe what she says she believed. The

data in Example 2A is not representative of the "Weizmann data she was aware of at that time." Example 2A has three molecular weight data points – 7.3, 8.4, and 22 kDa. These three data points do not provide any information between 8.4 and 22 kDa and cannot be representative of that data. The only data that we know Dr. Pinchasi actually had in front of her on the evening of May 24, 1994, was the April 1994 Data Table, which has thirteen data points showing *in vivo* mouse testing in which no mice died except for the mouse receiving copolymer-1 with an average molecular weight of 22 kDa. The thirteen batches included a 13 kDa batch and a 14.5 kDa batch, which she chose to include in the *in vitro* RBL section of Example 2B, but omit from the *in vivo* mouse section of Example 2A. (DTX 3149; July Tr. at 149:16-150:21 (Pinchasi).)

Had Pinchasi included the two *in vivo* mouse results, showing that no mice died at 13 kDa and 14.5 kDa, the Examiner could not have concluded that the claimed copolymer-1 exhibited unexpected results over the '550 patent, which described a copolymer-1 composition with an average molecular weight of 10 kDa.

625. Dr. Pinchasi similarly testified that Example 2B accurately reflects what she knew in 1994 and still believes today—that there is a correlation between the average molecular weight of copolymer-1 and toxicity measured by the *in vitro* RBL test set forth in Example 2. (July Tr. (Pinchasi) 130:5-131:8, 135:6-22.)

Sandoz's Response:

This proposed finding is misleading. The relevant inquiry is not whether Dr. Pinchasi believes that there is a correlation between the average molecular weight of copolymer-1 and toxicity measured by the *in vitro* RBL test set forth in Example 2. The patent claims are not directed at a correlation in general. They are directed to a copolymer-1 with specific ranges of molecular weight. The relevant inquiry is whether Dr. Pinchasi withheld material information from the PTO with an intent to deceive the Examiner that precluded the Examiner from knowing the data for the relevant ranges, which led to his allowing the claims.

Sandoz does not dispute that Dr. Pinchasi stated: "I believe today that there is a strong correlation between RBL degranulation and molecular weight, and a somewhat more complex correlation between in vivo toxicity and molecular weight of the copolymer-1 and that these should be taken into consideration when you go forward to develop and market a drug that is meant to treat patients for long term, for the duration of their life." (July Tr. 135:9-16.) But Dr. Pinchasi did not tell the PTO that there is a "strong correlation" between molecular weight and toxicity. She painted the story as a black and white, toxic versus non-toxic distinction between molecular weights below 8.4 kDa and those above 13 kDa; and she admitted that the concept of a "trend" or "probability" of lower toxicity at lower molecular weights was nowhere in the patent application. (July Tr. at 262:12-264:7.)

626. Dr. Pinchasi also testified that she believed then, and continues to believe, that the RBL degranulation test was sufficiently reliable and reproducible for the purposes for which it was used at Teva, including establishing the correlation between molecular weight and toxicity for copolymer-1. (July Tr. (Pinchasi) 95:13-20, 104:16-20.)

Sandoz's Response:

For the reasons stated above, this testimony is contradicted by what Dr. Pinchasi wrote in her 1989 memo and withheld from the PTO. It is also contradicted by the fact that the record only supports the use of RBL testing at Teva until 1992.

627. Dr. Pinchasi's testimony as set forth above was credible and supports a finding that she did not act with intent to deceive.

Sandoz's Response:

For the reasons stated above, the Court should find that Dr. Pinchasi did not testify credibly, and at all times in 1994, acted intentionally in providing a false black and white picture of the relationship between molecular weight and toxicity.

(2) Dr. Pinchasi's Documents Do Not Establish Good Faith

628. Dr. Pinchasi's testimony is corroborated by contemporaneous documents, which

establish that she truly believed that there was a correlation between molecular weight and toxicity for copolymer-1, and that it was necessary to lower the molecular weight range of copolymer-1 to approximately 5,000 to 9,000 daltons in order to have the best chance for an active, non-toxic product.

Sandoz's Response:

Teva calls these documents "contemporaneous" evidence of her good faith belief. In the inequitable conduct inquiry, Dr. Pinchasi's "good faith" belief must be measured at the time of her misconduct – May 1994 and after. These "contemporaneous" documents are all from six years earlier.

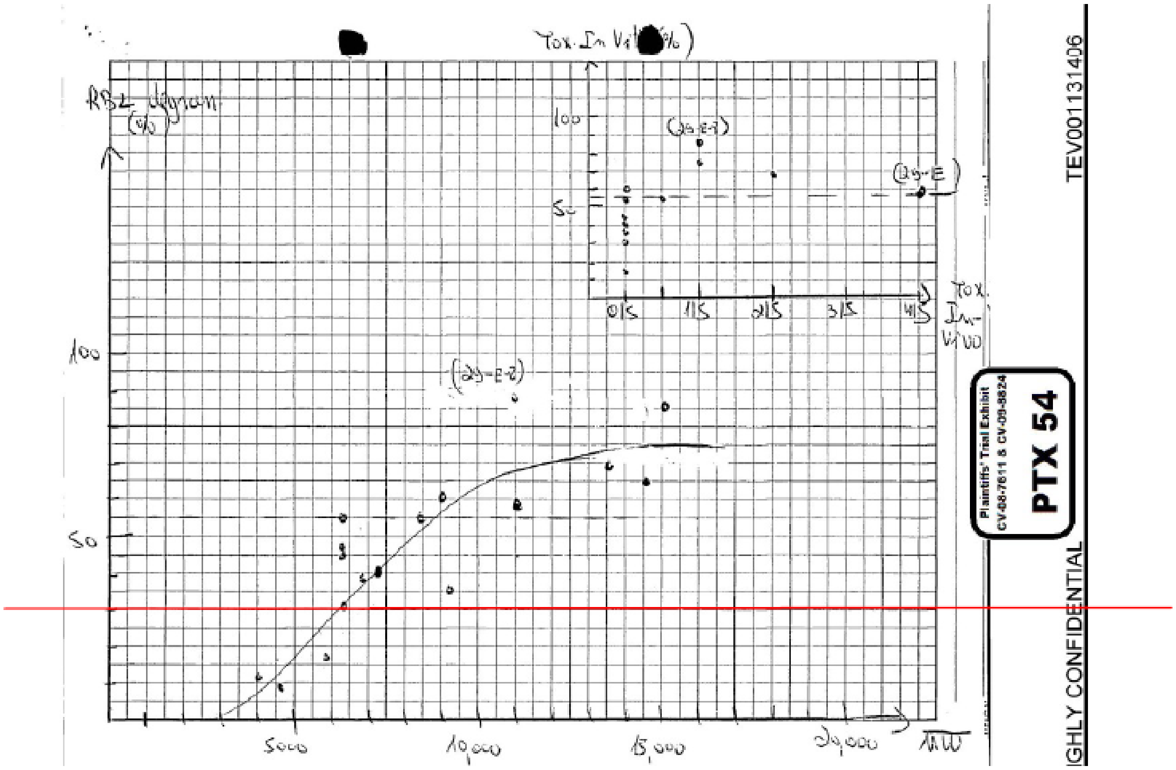
629. In particular, Dr. Pinchasi testified about a series of graphs she created in around April 1988 that demonstrated the correlation between molecular weight and toxicity that her team had discovered.

Sandoz's Response:

These graphs were created in 1988, six years before Teva filed its patent application in 1994. The 1988 graphs do not justify or explain Dr. Pinchasi's selective presentation and omission of information to the PTO in 1994.

630. For example, in the graph in the lower left hand corner of Figure 28 below, Dr. Pinchasi plotted RBL degranulation percent vs. molecular weight for several different copolymer-1 batches. As Dr. Pinchasi testified, and as can be seen in the graph, the data showed an almost linear correlation between molecular weight and toxicity. (July Tr. (Pinchasi) 46:21-48:24; PTX 54 at TEV001131406.)

Figure 28



Sandoz's Response:

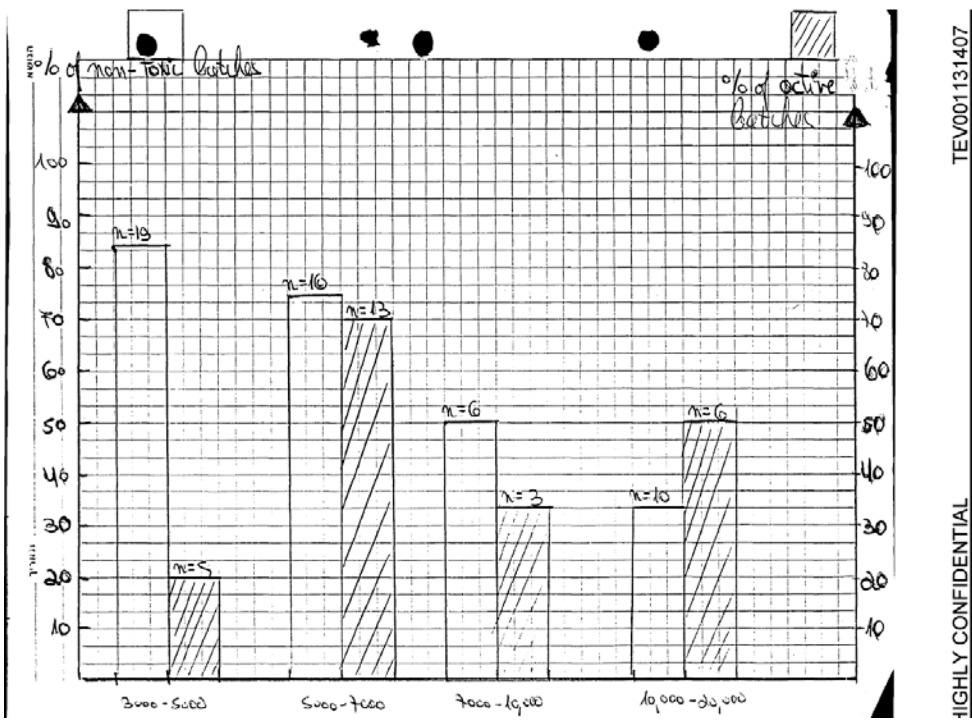
This chart highlights that Teva moved its RBL cutoff up and down to support whatever argument it wanted to make regarding the molecular weight and toxicity. The above figure appears to have a cutoff line drawn at 55% RBL degranulation. That cutoff is consistent with Dr. Pinchasi's testimony that the first toxic batch appears at 9,000 daltons. (July Tr. 48:25-49:4.) However, Dr. Pinchasi later testified that her cutoff for determining toxicity using the RBL assay was 30%. (July Tr. 58:8-13.) Using that cutoff, every batch of copolymer-1 with a molecular weight greater than 6,000 daltons was toxic. This changing cutoff for RBL-degranulation is consistent with Dr. Pinchasi's 1989 memo describing all of the problems with the RBL assay, including her belief that the RBL toxicity cutoff was arbitrary. (DTX 3385 at TEV001222392;

DTX 999A at TEV001222392-RC.) It is also consistent with Teva changing the RBL cutoff to support whatever particular "critical range" it was attempting to show at the time.

Regarding the "almost linear correlation between molecular weight and toxicity," Dr. Pinchasi did not tell the PTO that there was a linear correlation between toxicity and molecular weight. Instead, she painted the "black and white" picture described in more detail above.

631. In Figure 29 below, Dr. Pinchasi created a bar graph that plotted the percent of copolymer-1 batches that were non-toxic and active in different molecular weight ranges. As Dr. Pinchasi testified, and as the bar graph shows, the range from 5,000 to 7,000 daltons gave the highest proportion of batches that were both non-toxic and active. (July Tr. (Pinchasi) 51:20-53:19; PTX 54 at TEV001131407.)

Figure 29



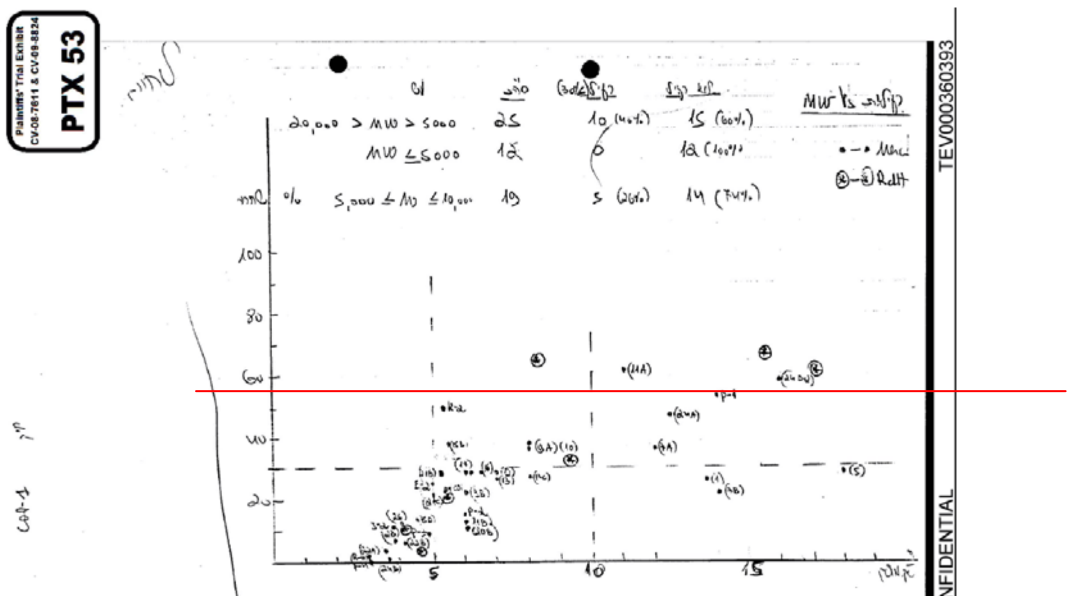
Sandoz's Response:

Teva cites a bar graph that supposedly shows a correlation between toxicity and activity. Teva's "unexpected results" arguments throughout the prosecution history discuss a correlation between molecular weight and toxicity. They say nothing about a correlation between toxicity

and activity. Figure 29 and the accompanying testimony cannot support Dr. Pinchasi's good faith basis for withholding information related to toxicity.

632. Dr. Pinchasi also testified about the plot of RBL degranulation percent vs. molecular weight for several batches of copolymer-1 shown in Figure 30 below. (July Tr. (Pinchasi) 57:2-61:13; PTX 53 at TEV000360393; PTX 53-T at TEV000360393.) This graph again showed that there was a correlation between molecular weight and toxicity, and that a molecular weight range of 5,000 to 9,000 daltons provided the best chance for a batch of copolymer-1 to be active and non-toxic. (July Tr. (Pinchasi) 57:15-59:23.)

Figure 30



Sandoz's Response:

This graph is another example of Teva arbitrarily moving the RBL cutoff to support its contention that it found a particular range of low toxicity. To justify a finding that the "non-toxic" molecular weight range is between 5,000 and 9,000, Dr. Pinchasi had to drop the RBL cutoff from 55% in PTX 54 to 30% in PTX 53. Using the 55% cutoff from PTX 54, nearly every batch up to 14 kDa is not toxic. This is not evidence consistent with discovering a "critical range" of low molecular weight and non-toxicity. Rather, it is evidence that one must arbitrarily move the RBL cutoff to support a finding that a there is a non-toxic, high activity range of molecular weights below the 10 kDa limit set by the prior art.

633. In fact, Defendants' expert Dr. Kimber agreed with Dr. Pinchasi's assessment that the graph in Figure 30 above shows a trend in the data of increasing toxicity with increasing molecular weight. (July Tr. (Kimber) 429:10-430:8.)

Sandoz's Response:

The patents-in-suit say nothing about a "trend" of increasing toxicity with increasing molecular weight. Dr. Pinchasi's belief in a position not taken with the PTO is not relevant to whether she intended to deceive the PTO.

634. Dr. Pinchasi reported these conclusions in contemporaneous memoranda and correspondence. For example, in a May 1988 status report, Dr. Pinchasi reported that the molecular weight range of 15,000 to 25,000 daltons that had been used in the past by the Weizmann researchers yielded a majority of batches that were toxic in the RBL degranulation test, and that "the optimum range for an active and nontoxic material is 6000-9000." (July Tr. (Pinchasi) 39:18-41:24; PTX 41 at 2.)

Sandoz's Response:

The memoranda are not "contemporaneous" with the alleged act of inequitable conduct in 1994.

635. Similarly, in an April 14, 1988 memo, Dr. Pinchasi characterized low-molecular weight (3,000-6,000 daltons) batches of copolymer-1 as "non-toxic" and high-molecular weight (10-25,000 daltons) batches as "toxic." (PTX 35 at TEV000360388; PTX 35-T at TEV000360388; July Tr. (Pinchasi) 43:21-45:6.)

Sandoz's Response:

This document actually refutes any belief that Dr. Pinchasi thought at that time that there was a correlation between molecular weight and toxicity. In the memo, Dr. Pinchasi is complaining that reagents from various suppliers are making some batches come out as 3,000-6,000 daltons, and other batches come out as 10-25,000 daltons. Pinchasi states that her goal is to produce copolymer-1 like the one used in the Bornstein clinical trials, which she describes as "high molecular weight, but on the other hand non-toxic."

> The reagent being used - HBr in glacial acetic acid- is critical: the same reagent - from various suppliers - gives a different final product: low-molecular (3000-6000) and non-toxic- as opposed to

> high molecular (10-25,000) and toxic. The purpose of our research is to find conditions in which we may obtain a material which is similar to the one that was used in the clinical trials, in other words, high molecular weight, but on the other hand non-toxic.

(PTX 35-T at TEV000360388.) Thus, according to Pinchasi's own words, she did not believe in 1988 that the toxicity of copolymer-1 was related to molecular weight, as both high molecular weight and low molecular weight batches could be non-toxic.

636. In a June 27, 1988 quarterly report, Dr. Pinchasi reported that "[a]n unequivocal correlation was found between molecular weight and in vitro toxicity of COP-1: the higher the molecular weight-the more toxic is the drug. This relationship was correlated on several batches prepared both at the Weizmann Institute and at Bio-Yeda." Dr. Pinchasi concluded in the report that "[i]n order to produce a nontoxic material, its molecular weight should be < 10,000 and not 15,000 to 25,000 as declared in the Bio-Yeda chemical file (submitted to the FDA February of '86)." (July Tr. (Pinchasi) 69:1-71:10; PTX 40 at 1.)

Sandoz's Response:

This is yet another example of Teva supporting Dr. Pinchasi's choice to withhold information from the PTO by pointing to documents supporting an argument that Teva did not make to the PTO. Teva could not overcome a prima facie case of obviousness by pointing to a general correlation between molecular weight and toxicity. As described in more detail in Section X (Obviousness), *infra*, Teva had to show that it discovered a "critical range" demonstrating unexpected results over the prior art. As explained above, Dr. Pinchasi did not disclose this belief in a general correlation to the PTO, and she did not disclose the data on which she relied for this belief.

637. In a July 25, 1988, letter to Dr. Bornstein, Dr. Pinchasi similarly reported that Teva had "found a very strong positive correlation between molecular weight and toxicity" that was "unequivocal." (July Tr. (Pinchasi) 71:25-74:3; PTX 42 at 1.)

Sandoz's Response:

See Sandoz's response to the previous proposed finding.

638. These conclusions were later summarized in a 1991 report by inventor Mr. Konfino: "In the early period of development the data on the many samples of COP-1 . . . were

gathered together and the distribution of their toxicity and bio-activity versus the molecular weight were laid down on a milimetric paper. It was found that the largest number of satisfactory samples were crowded in the relatively narrow section between molecular weight 5000-7000. The specification for MW of COP-1 was thus fixed as 6000±1000 . . ." (July Tr. (Pinchasi) 79:14-81:22; PTX 708 at TEV000324552; PTX 708-T at TEV000324552.)

Sandoz's Response:

Here, Mr. Konfino is just summarizing Pinchasi's work from 1988. Konfino's summary does not have any bearing on whether Dr. Pinchasi committed inequitable conduct in 1994.

(3) Dr. Pinchasi's Motive to Lie to the PTO

639. Defendants have asserted that Dr. Pinchasi had a motive to lie to the PTO because she needed to obtain a patent covering Copaxone® in order to bring the product to market. The evidence is to the contrary.

Sandoz's Response:

Teva provides no cite for the proposition that Sandoz has ever stated that Pinchasi lied to the PTO because she needed to get a patent in order to bring Copaxone to the market. All of Teva's proposed facts regarding Pinchasi's motives are irrelevant and designed to refute an argument that Sandoz did not make.

Proving a motive to lie is not an element of an inequitable conduct defense. Regardless, Teva, represented by the same law firm who tried this case for Teva, told the U.S. Supreme Court on September 29, 2010, the following regarding why a patent applicant, like Dr. Pinchasi, would lie to the PTO:

- "Despite the disclosure obligation imposed on patent applicants, a rational patent applicant will recognize that the benefits of concealing material information often exceed the costs. The principal benefit is a higher likelihood of obtaining an issued patent." (p. *7)
- "An issued patent is often extremely valuable even if the patent is ultimately found to be invalid." (p. *7)
- "[T]he economic incentive to obtain by any possible means even an exceptionally weak patent covering a commercial drug product is very great indeed." (p. *9 n.5)

- "Under current Federal Circuit law, once a patent issues, potentially invalidating information concealed from the examiner becomes much less of a threat to the patent." (p. *9)
- There is a "powerful incentive to conceal potentially invalidating prior art and other information during patent prosecution. It would be naïve to assume that applicants rarely succumb to such temptations." (p. *10)
- "Since most of the conversations between inventors and patent counsel during the actual prosecution will be protected by the attorney-client privilege, contemporaneous evidence of actual motivation will often not be discoverable, and the ability of patentees to articulate plausible post hoc rationalizations for decisions made years earlier during patent prosecution makes proof of intent to deceive by clear and convincing evidence a formidable task for any defendant." (p. *13)
- "[T]he Federal Circuit's requirement that invalidity be proven by clear and convincing evidence, even where material, non-cumulative information was not before the examiner, encourages patent applicants to ignore or conceal information critical to informed patent examination." (p. *14)

(Brief of Amicus Curiae Teva Pharmaceuticals USA, Inc., *Microsoft Corp. v. I4I Ltd. P'ship*, No. 10-290, 2011 WL 380830 (U.S. Sup. Ct. filed Feb. 2, 2011).)

Applying Teva's beliefs to the facts of this case, if Dr. Pinchasi were a "rational patent applicant," then she would "recognize that the benefits of concealing material information often exceed the costs." In other words, when providing and selecting the toxicity information, Dr. Pinchasi would recognize that the benefits of withholding the inconsistent toxicity information exceeded the costs. That is true. Teva's enjoyed a patent monopoly on Copaxone since its launch in 1997 and will have enjoyed over $10 billion in Copaxone sales before this Court will have a chance to invalidate its patents.

Similarly, applying Teva's own beliefs about the behavior of patent applicants, Dr. Pinchasi had a "powerful incentive to conceal potentially invalidating prior art and other information during patent prosecution." Moreover, it "would be naïve to assume that applicants [*i.e.*, Dr. Pinchasi would] rarely succumb to such temptations."

640. As Dr. Pinchasi testified, when Teva began work on the copolymer-1 project, it knew that the Weizmann Institute's '550 patent on copolymer-1 was going to expire before a product could be brought to market. Teva decided to proceed with the project anyway, because it developed strategies that it believed could protect exclusivity in the marketplace even without having a patent on the product. (July Tr. (Pinchasi) 19:12-22:3, 117:22-118:8.)

Sandoz's Response:

The evidence shows that Dr. Pinchasi was so dedicated to getting a patent that she ordered three employees to stay at Teva until 2:00 a.m. one night to get an application on file. (PTX 1389 at 55:22-56:9, 81:1-5 (Haber); PTX 1390 at 21:55-23:4 (Haber).)

Teva's willingness to launch a product without patent protection has no logical bearing on whether it later valued getting a patent on the product or whether Dr. Pinchasi intended to deceive the PTO. Whether it was "icing on the cake" or crucial to protecting its investment, Dr. Pinchasi wanted a patent enough to stay at work until 2:00 a.m. to prepare a patent application for filing in another time zone by lawyers on another continent in order to preserve Teva's ability to obtain patents. (PTX 1389 at 55:22-56:9, 81:1-5 (Haber); PTX 1390 at 21:55-23:4 (Haber); July Tr. 203:18-22 (Pinchasi).)

641. Teva assumed that copolymer-1 would be entitled to orphan drug exclusivity, which was established by the U.S. government to encourage pharmaceutical companies to develop drugs for diseases with fewer than 200,000 patients. Orphan drug exclusivity provides seven years of exclusivity from the time a product reaches the market regardless of whether the product is covered by a patent. Teva was in fact eventually awarded orphan drug exclusivity for Copaxone®. (July Tr. (Pinchasi) 20:22-21:23; PTX 41-A at 5.)

Sandoz's Response:

Whether Teva thought it could get seven years of orphan drug status has no bearing on whether it also wanted the significantly longer patent term. Teva appears to be claiming that it invented the improved copolymer-1 in 1988. With its patents expiring in 2014 or 2015, Teva's patent monopoly is set to extend up to 27 years from the date of invention.

642. Teva also knew that copolymer-1 would be difficult to manufacture reproducibly in a commercial pharmaceutical context. (July Tr. (Pinchasi) 19:23-20:21.)

Sandoz's Response:

Undisputed because Teva is attempting to protect its Copaxone franchise by impermissibly relying on both trade secret and patent protection.

643. Moreover, there is no evidence that the lack of patent protection for copolymer-1 was ever an issue during development of Copaxone®. On the contrary, the evidence showed that Teva was prepared to go to market with Copaxone® without patent protection.

Sandoz's Response:

Even if Teva planned to go forward without patent protection, it does not follow that it was unwilling to bend the rules to get patent protection.

644. As Dr. Pinchasi testified, she could not remember the subject of patent protection ever coming up at a meeting concerning the development of copolymer-1. (July Tr. (Pinchasi) 117:18-21, 118:20-25.)

Sandoz's Response:

The proposition that a company with an in house patent department never considered getting a patent on its first innovative drug lacks common sense and credibility. Neil Nachshen testified that before May 24, 1994, his job responsibility was to file a patent application on copolymer-1 and that he was told "that I should liaise with Irit about" it. (PTX 1393 (Nachshen Depo.) at 28:25-29:12.) On May 24, 1994, he went to Dr. Pinchasi's office, specifically asking her about publications that would affect patent rights. (DTX 1394 (Nachshen) at 25:1-27:6.) This meeting took place nearly three years before Teva launched Copaxone on April 2, 1997. (Teva Proposed Finding 15.)

645. Dr. Pinchasi's testimony was corroborated by her handwritten memo summarizing a June 5, 1991 discussion concerning a copolymer-1 Go/No Go meeting. (July Tr. (Pinchasi) 106:20-24, 118:20-121:22; PTX 57; PTX 57-T.) As Dr. Pinchasi testified, in Teva's terminology a Go/No Go meeting was a meeting at which a decision was taken on whether to abort a project or continue development. (July Tr. (Pinchasi) 106:20-24.) Dr. Pinchasi's memo contained a thorough list of all of the critical issues that existed at that time with respect to the development of copolymer-1. Lack of patent protection for copolymer-1 was not mentioned in the memo and was not discussed at the Go/No Go meeting. (July Tr. (Pinchasi) 118:20-121:22; PTX 57; PTX 57-T.)

Sandoz's Response:

By 1994, Teva had a strong interest in obtaining patent protection, as evidenced by Dr. Pinchasi ordering a team of people to stay at work until 2:00 a.m. to get it done. (PTX 1389 at 55:22-56:9, 81:1-5 (Haber); PTX 1390 at 21:55-23:4 (Haber); July Tr. 203:18-22 (Pinchasi).)

646. Significantly, at the time Teva filed its NDA for Copaxone® it did not have an issued patent, and it did not know whether it would ever have patent protection for the product. (July Tr. (Pinchasi) 118:9-19.)

Sandoz's Response:

By 1994, Teva had a strong interest in obtaining patent protection, as evidenced by Dr. Pinchasi ordering a team of people to stay at work until 2:00 a.m. to get it done. (PTX 1389 at 55:22-56:9, 81:1-5 (Haber); PTX 1390 at 21:55-23:4 (Haber); July Tr. 203:18-22 (Pinchasi).)

647. Dr. Pinchasi's lack of motive to withhold the April 1994 Data Table from the PTO is further demonstrated by the fact that the claims in the '037 patent application when Dr. Pinchasi reviewed it on the night of May 24, 1994 did not have any average molecular weight limitations. They were directed, instead, to the percent of species above 40 kilodaltons or the percent of species between 2 and 20 kilodaltons. The April 1994 Data Table, on the other hand, had average molecular weight information, but no information about percent species in those ranges. The April 1994 Data Table, therefore, would not have contained any information relevant to the patentability of those claims. (July Tr. (Pinchasi) 131:20-132:8; July Tr. (Kimber) 478:4-15; DTX 3149T; PTX 10 at TEV003009937.)

Sandoz's Response:

See Sandoz's Response to ¶ 569.

(4) Dr. Pinchasi Took Inconsistent Positions With the FDA and PTO

648. Defendants assert that Dr. Pinchasi's intent to deceive is demonstrated by the fact that she took different positions concerning molecular weight and toxicity before the PTO and the FDA. The evidence was otherwise.

Sandoz's Response:

Sandoz sets forth specific responses below, but notes that Teva's inconsistencies between what it told the PTO and FDA were not limited to the toxicity of copolymer-1. As Sandoz set forth in its opening brief, Teva told different stories when it came to the underlying data in the

Bornstein BR-1 clinical studies. When trying to rely upon the BR-1 studies to support its NDA, Teva told the FDA that its copolymer-1 was similar to the Bornstein BR-1 copolymer-1 and that the molecular weight of the Bornstein BR-1 copolymer-1 was as low as 10.35 kDa. (*See* Sandoz's FFCOL ¶¶ 193-197, 200, 215-16, 304.) To the PTO, however, Teva submitted only the Bornstein papers, which stated that the molecular weight was 14-23 kDa. (PTX 31.)

649. Neither Dr. Pinchasi nor Teva took a position with the FDA that contradicted or was inconsistent with the toxicity data in Example 2 of the patents-in-suit.

Sandoz's Response:

One example of an inconsistency in positions taken with the FDA and the PTO is that Teva told the FDA that its copolymer-1 was safe and effective in the molecular weight range of 4,700 to 13,000, by applying for FDA approval of copolymer-1 in its original NDA for Copaxone. (July Tr. 85:23-86:3.) To the PTO, Teva said in Example 2B that a batch of copolymer-1 with an average molecular weight of 13,000 daltons was toxic. (PTX 1, '808 patent, col. 4:11-27.) (*See also* Sandoz's FFCOL ¶¶ 303-307.)

650. Teva represented to the FDA that the low average molecular weight copolymer-1 compositions were, in certain respects, comparable to the high average molecular weight copolymer-1 compositions used by Dr. Bornstein in his clinical trial. Teva's statements to the FDA about *safety*, however, are not inconsistent with what Teva told the PTO about the *toxicity* of high molecular weight copolymer-1.

Sandoz's Response:

Teva's statements to the PTO in Example 2 applied to both "safety" of copolymer-1 and the "toxicity" as measured by in vivo mouse and in vitro RBL tests. Dr. Pinchasi described the "safety" of copolymer-1 in the context of local injection site reactions and other systemic reactions. (July Tr. 24:2-23.) Example 2 referred to these safety concerns, noting that the RBL test was "used in order to screen out those batches of copolymer-1 which invoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (PTX 1 at

col. 3:63-67.) Teva pretends that only toxicity in the context of mouse and RBL testing is discussed in the patents-in-suit. However, safety is discussed, as well.

651. As Defendants' expert Dr. Green testified, safety and tolerability are two different concepts. Dr. Green explained that two drugs can be equally safe, yet have different tolerability profiles. (PTX 881 (Green Dep.) at 16:12-17:04.)

Sandoz's Response:

Sandoz takes no position regarding a deposition for which it was not noticed and did not attend other than to say that safety and tolerability are different, but both are related to side effects. Safety refers to whether the drug has side effects that are dangerous to the patient. Tolerability refers to how well the patient deals with side effects. (Sept. Tr. 100:23-101:6 (Lisak).) Example 2 addresses side effects and is therefore relevant to both safety and tolerability.

652. The local and systemic side reactions that the toxicity testing in the patent are intended to screen for are related to the *tolerability* and *not the safety* of copolymer-1. (July Tr. (Arnon) 315:7-15; July Tr. (Pinchasi) 26:2-14; PTX 881 (Green Dep.) at 16:12-25.)

Sandoz's Response:

This proposed finding is contradicted by Dr. Pinchasi's testimony equating "safety" with systemic side effects:

> Q. Did you learn anything about the side effects that Dr. Bornstein found in the trial?
>
> A. Of course, you cannot have efficacy without some safety issues. And we understood that there were mainly two types of adverse events. The first type are the local injection-site reaction. We are talking here about patients injecting daily a drug that is a key polymer of acid subcutaneously for two years. That was the duration of the study. So you would expect some injection-site reactions. And these were reddening and swelling and some pain at the injection site.
>
> And the second type of reactions were more systemic reactions which, for lack of a better name . . .

(July Tr. 24:2-13 (Pinchasi).)

653. As Dr. Green acknowledged, Teva did not make any representations to the FDA that the *tolerability* of low average molecular weight copolymer-1 was the same as the prior art high average molecular weight copolymer-1. (PTX 881 (Green Dep.) at 17:1-4, 111:11-24.)

Sandoz's Response:

Sandoz takes no position regarding a deposition for which it was not noticed and did not attend other than to say this is irrelevant. Teva's comments to the FDA and PTO are inconsistent whether categorized as "safety" or "tolerability." To the FDA, Teva was seeking permission to market copolymer-1 with a molecular weight of up to 13 kDa, but to the PTO, Teva was arguing that copolymer-1 with a molecular weight of less than 10 kDa had unexpectedly superior toxicity compared to copolymer-1 with a molecular weight greater than 10 kDa. Common sense dictates that these positions are inconsistent.

654. Moreover, the Bornstein article, which was incorporated by reference in the specification of the patents-in-suit, described the use of high average molecular weight copolymer-1 in human patients and stated that it was shown to be non-toxic in animal studies. (PTX 1, col. 1:25-28; PTX 31 at 4081.) Thus, the PTO was aware that high molecular weight copolymer-1 was "safe" for use in humans.

Sandoz's Response:

As noted above, Teva provided the FDA and PTO different information regarding the molecular weight ranges in the BR-1 Bornstein trials. In addition, Teva highlighted for the FDA that the Bornstein BR-1 copolymer-1 was more comparable to its copolymer-1 than would appear from the molecular weights on their face, because the Bornstein batches were measured with ultracentrifugation, resulting in higher value weight average molecular weights, whereas its batches were expressed as lower value peak molecular weights using SEC. Teva never explained the same to the PTO. Moreover, Teva did not provide the PTO with a copy of the Bornstein paper until seven of the nine patents had already issued. Were the Court nonetheless to presume that the PTO was aware that higher molecular weight copolymer-1 was as safe in

humans as lower molecular weight copolymer-1, this constitutes clear and convincing evidence that the PTO erred in issuing the patents-in-suit. The patents were *prima facie* obvious, and Teva could not overcome the *prima facie* obviousness if Teva's claimed copolymer-1 showed no unexpected results over Bornstein.

C. Conclusions of Law

655. In order to prove that Dr. Pinchasi committed inequitable conduct, Defendants bear the burden of proving both materiality and intent to deceive by clear and convincing evidence. They have failed to do so.

Sandoz's Response:

Sandoz agrees that it has the burden of proof, but it met that burden.

(i) The Materiality of the April 1994 Data Table and the RBL Degranulation Information

656. As an initial matter, Defendants are required to prove materiality under the "but-for" standard articulated in *Therasense*. 2011 WL 2028255, at *12. Defendants have not alleged any affirmative misconduct on the part of Dr. Pinchasi. Their only claim is that she withheld information from the PTO. As a matter of law, the withholding of information cannot amount to an "exceptional case" involving "affirmative acts of egregious misconduct." *Id.* at *12-13.

Sandoz's Response:

The "but-for" standard is one of two ways to prove inequitable conduct under *Therasense*. The other way is to show that the patentee engaged in affirmative acts of egregious misconduct. Evidence of both were presented at trial.

Teva continues to misstate the holding of *Therasense* regarding the "affirmative acts of egregious misconduct" prong by claiming it does not encompass the withholding of secret, inconsistent test data. When discussing the "affirmative acts of egregious misconduct prong," the *en banc* Court in *Therasense* noted: "Because neither mere nondisclosure of *prior art references* to the PTO nor failure to mention *prior art references* in an affidavit constitutes affirmative egregious misconduct, claims of inequitable conduct that are based on such

omissions require proof of but-for materiality." (*Therasense*, Slip op. at 29-30 (emphasis added).) This limitation applies only to the nondisclosure of "prior art references." Teva is attempting to broaden the exception to the exception so as to exclude "information" in addition to "prior art." The Federal Circuit did not exclude the non-disclosure of all "information." The Federal Circuit's distinction makes sense, as PTO examiners have at least a chance of discovering withheld prior art as part of their duties to search for prior art. Examiners have no chance of finding the type of information withheld by Dr. Pinchasi (unfavorable internal data that is inconsistent with the favorable internal data presented to the PTO and the company's internal doubts about the scientific arguments it made in support of patentability). Accordingly, Dr. Pinchasi's withholding of "information" can be an "affirmative act of egregious misconduct."

657. To prove materiality under the "but-for" standard, Defendants were required to prove that the PTO office would not have allowed at least one claim in each of the patents-in-suit to issue had it been aware of the April 1994 Data Table and Dr. Pinchasi's views on the RBL degranulation test. *Id.* at *12.

Sandoz's Response:

This is another major misstatement of the holding in *Therasense*. There is no requirement in *Therasense* that Sandoz show "the PTO office would not have allowed at least one claim in each of the [nine] patents-in-suit." Sandoz need only show that one claim of one patent would not have issued "but for" the inequitable conduct. *Therasense* did not strip from district courts the authority to fashion an equitable remedy commensurate with the scope of the misconduct. *Therasense*, 649 F.3d at 1292.

658. Under Defendants' theory, the allegedly withheld toxicity information is related to the issue of unexpected results, which is a secondary consideration of non-obviousness. Unexpected results, however, are only relevant once a claim has been demonstrated to be *prima facie* obvious in view of the prior art. *See In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992) ("If examination at the initial stage does not produce a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent." (citations omitted)); *In re Fischer*,

484 F.2d 961, 963-64 (C.C.P.A. 1973) (holding that appellant need not show unexpected results because Patent Office failed to make out a prima facie obviousness case).

Sandoz's Response:

See Sandoz's Response to ¶ 577.

659. Thus, to establish that the April 1994 Data Table and other information were material to the claims of the patents-in-suit, Defendants were first required to introduce evidence proving that the claims were *prima facie* obvious. This obviousness analysis must be performed on a claim-by-claim basis and from the viewpoint of a person of ordinary skill in the art. 35 U.S.C. § 282; *KSR Int'l Co.*, 550 U.S. at 406.

Sandoz's Response:

Therasense does not proscribe the order of proof at trial. The Court did not instruct the parties that all overlapping issues must be presented solely in the first phase of trial. Teva cites no authority for the proposition that the Court cannot consider evidence from the entire of trial to decide the issue of inequitable conduct.

Sandoz presented evidence that the claims were prima facie obvious during both phases of trial. All patents were admitted into evidence. (PTX 1-9.) All prosecution histories were admitted. (PTX 10-21.) To prove that the claims were *prima facie* obvious, Sandoz presented clear and convincing evidence that the patent claims have the same chemical composition as the prior art and that the patent claims are expressed in ranges falling within and/or adjacent to the range recited in the prior art. *See In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955); *In re Hill*, 284 F.2d 955, 959 (C.C.P.A. 1960); *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782-83 (Fed. Cir. 1985); *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997). Sandoz proved during the July phase that both the prior art and the patents-in-suit were directed to the same chemical composition – copolymer-1. (*E.g.*, PTX 1, '808 patent, col. 1: 32-44 (Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine . . . . The present

invention relates to a composition of copolymer-1 . . . .); PTX 26,[6] '550 patent, col. 2:19-22 ("A preferred copolymer according to the present invention comprises in combination alanine, glutamic acid, lysine and tyrosine. . . .").) A review of the asserted claims shows that they are expressed in ranges falling within and/or adjacent to the range recited in the prior art. This is clear and convincing evidence establishing a *prima facie* case of obviousness.

660. Defendants, however, introduced *no* competent expert testimony during the inequitable conduct trial that any one of the asserted claims would have been found *prima facie* obvious in view of the prior art. Instead, Defendants ask the Court to make obviousness determinations based solely on attorney argument regarding the prosecution history. Attorney argument, however, is insufficient. *See Invitrogen Corp. v. Clontech Labs.*, 429 F.3d 1052, 1068 (Fed. Cir. 2005). In any event, as discussed above, the prosecution history does not support Defendants' contentions.

Sandoz's Response:

Expert witnesses "may" testify if "scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence…" Fed. R. Evid. 703. Expert witnesses are not required to aid the court in determining, for example, whether the molecular weight range of "about 5 to 9 kDa" is adjacent to the range of "10 to 25 kDa."

Teva's reliance on *Invitrogen* is misplaced. That case involved an invention related to genetically modifying the enzyme reverse transcriptase ("RT") to affect how the modified RT participates in DNA replication. *Id.* at 1058. The evidence relied on by Clontech was a series of laboratory notebooks reflecting the development of numerous different mutants over a series of years. *Id.* at 1068. Rather than presenting expert testimony to interpret these lab notebooks and explain their significance to one of skill in the art, Clontech's expert merely provided a conclusory opinion on the ultimate legal issue of conception. *Id.* It was this failing that the Federal Circuit criticized in *Invitrogen*, noting that Clontech could not remedy the absence of expert testimony interpreting the complex data by copious legal argument. *Id.* In doing so, the

[6] During the July phase, the '550 patent was admitted as DTX 1219.

Court did not create a requirement that all facts must be supported by expert testimony, even facts obvious on their face. Rather, the Federal Circuit simply reiterated that, where specialized knowledge is required, it must come through expert testimony, not legal argument. Determining whether 9.9 is next to 10 requires no such specialized knowledge.

Furthermore, Sandoz did present expert testimony on these issues. Mr. Rzucidlo testified that patent examiners would determine whether the claims were prima facie obviousness by applying the M.P.E.P. guidelines, which instruct examiners to issue prima facie obviousness rejections when claims are drafted to the same chemical compositions with adjacent ranges of properties. (*See* Sandoz's FFCOL ¶ 315.) The evidence also includes the testimony of Drs. Rice and Zeiger, who gave extensive testimony of obviousness. (*See* Sandoz's FFCOL ¶¶ 190-227.)

661. Defendants' failure of proof precludes a finding that the allegedly withheld information was material.

Sandoz's Response:

There is no failure of proof.

662. Even if the toxicity data in the patent were required to establish the patentability of any claim of the patents-in-suit (which they are not), the April 1994 Data Table and Dr. Pinchasi's views on the RBL degranulation test would not be material because they are consistent with, and therefore cumulative of, both Example 2 of the patents and other information provided to the PTO during prosecution. *See Honeywell Int'l Inc. v. Universal Avionics Sys. Corp.*, 488 F.3d 982, 1000 (Fed. Cir. 2007).

Sandoz's Response:

For the reasons stated above, the record proves that the withheld information was inconsistent with the information provided to the PTO. The April 1994 Data Table was not cumulative of the data in the patent. It specifically showed toxicity values just above and below 10 kDa, which is where the prior art leaves off and the patent scope allegedly begins. The patent provides toxicity data at 8.4 kDa and 13 kDa, but nothing in between.

663. The April 1994 Data would also not be material because it represents only a small

fraction of Teva's data, and Teva's data as a whole is consistent with Example 2. (July Tr. (Arnon) 332:8-334:2; July Tr. (Pinchasi) 30:14-20, 80:13-81:13; July Tr. (Baird) 601:13-24; PTX 887.)

Sandoz's Response:

The April 1994 Data Table was highly material because it included toxicity information at the border of where the "critical range" ends and the prior art begins. Example 2 in the patent included one data point at 8.4 kDa and one at 13 kDa. But to get the patent, Teva claimed a range up to 9.9 kDa and had to distinguish anything 10 kDa and greater. The April 1994 Data Table included seven additional data points between 9.25 and 12.15 kDa. That additional data told a different toxicity story than portrayed by Example 2. For example, no mice died in any of the omitted batches, proving that there was no toxicity in those batches. Similarly, if the labelled "outliers" are excluded, none of the RBL values showed toxicity, depending on which RBL cutoff one applies.

664. Moreover, even if Dr. Pinchasi did have reservations about the RBL degranulation test, there is no evidence those reservations were shared by anyone else. To the contrary, the evidence shows that the RBL degranulation test is a widely accepted test in the scientific community, including by Defendants' own scientists, and the description of it in the patent is in line with both how it was used at Teva and the Weizmann Institute, and how the literature had reported that it could be used. Significantly, inventor Professor Arnon personally held the view then, and still holds the view, that the test is reliable and reproducible enough to screen batches of copolymer-1 for toxicity. (July Tr. (Pinchasi) 286:11-288:16; July Tr. (Arnon) 320:7-321:18, 327:22-331:4; July Tr. (Kimber) 466:20-468:21, 471:16-18, 472:4-475:6; PTX 31 at 409; DTX 1334 at 345.)

Sandoz's Response:

Teva claims that "there is no evidence [Dr. Pinchasi's] reservations were shared by anyone else." That is false. Mr. Konfino shared the same view and thought there was a "serious problem" with the RBL test. In his September 1988 Research and Development report (DTX 3059 (translated)), Mr. Konfino includes a section called "Toxicity Test" in which he described the RBL test. (DTX 3059 at TEV000419246.) Mr. Konfino, like Dr. Pinchasi, concludes,

"There is a serious problem with the biological test methods, due to their lack of reproducibility." (*Id.*)

Dr. Pinchasi was not alone in her views. She was the person with overall responsibility for the copolymer-1 project at Teva. She signed her name under the "Approved" block of the official company document assessing the RBL test. (DTX 3385 at TEV001222392; DTX 999A at TEV001222392RC.) She agreed that the document was "quite formal at Teva" and "submitted to the FDA." (July Tr. 213:5-11.) This constitutes clear and convincing evidence that Pinchasi's evaluation of the application of the RBL test to copolymer-1 was shared by all others at Teva. Regarding Dr. Arnon, as stated above in response to Teva's Proposed Finding No. 612, Teva misstates Dr. Arnon's testimony about her present belief regarding the RBL test. Moreover, Dr. Arnon was not identified as an inventor of the patents-in-suit when the inequitable conduct occurred. (PTX 11 at TEV000309434.) There is no case law allowing a party to avoid inequitable conduct by adding an inventor (Arnon, an employee of the Weizmann Institute, not Teva) who lacked knowledge of the inequitable conduct. Moreover, substituting Arnon as an inventor for Pinchasi made no difference because Konfino shared the same reservations as Pinchasi.

665. If the literature, such as the Barsumian article, which is cited in the patent itself, reports that the RBL test with a precision of ±20% is reliable and reproducible, and the inventor herself believes this to be the case, it is not plausible that Dr. Pinchasi's personal views would have prevented any of the claims from issuing.

Sandoz's Response:

The Barsumian paper says nothing about Teva's use of the RBL test to assess toxicity of copolymer-1. Pinchasi's views were specific to copolymer-1. If the Examiner were told that Teva's RBL data for copolymer-1 submitted to the PTO was not reproducible and had an

arbitrary cutoff, the Examiner would have rejected any arguments of unexpected results based on that data.

666. Finally, even if the RBL degranulation test data was not sufficiently reproducible to be relied upon (a conclusion the Court is not reaching), Defendants presented no evidence that the *in vivo* mouse data in Example 2 would have been insufficient to demonstrate the patentability of any claim of the patents-in-suit. In fact, Defendants presented no expert testimony at all regarding the *in vivo* mouse assay during the July 2011 trial. Defendants' expert Dr. Rice testified only during the September 2011 trial and, as the Court ruled during trial, Dr. Rice's testimony could not be relied on to prove inequitable conduct. (Sept. Tr. (Rice) 1029:7-20, 1032:8-21.)

Sandoz's Response:

Teva misses the point on Sandoz's inequitable conduct defense. Teva withheld toxicity data that would have changed the Examiner's decision to issue the claims. The inquiry is not limited to what was *presented* to the PTO. The inquiry focuses on what was *withheld* from the PTO. The April 1994 Data Table has 13 data points of *in vivo* mouse data. That was part of the evidence in the July trial phase. No expert testimony is needed to see that no mice died until the copolymer-1 reached 22 kDa. No mice dying until 22 kDa is inconsistent with the claim that the copolymer-1 in the claimed invention was "improved" over the prior art, which described copolymer-1 as low as 10 kDa.

Regarding Dr. Rice, respectfully asks the Court not to consider it just because the trial was divided into two phases. To the extent that the Court finds Dr. Rice's testimony helpful in understanding the evidence, the Court should consider it. Teva had ample opportunity to cross examine Dr. Rice and make any arguments it wants based on her testimony.

667. Thus, Defendants have failed to prove by clear and convincing evidence that any of the information or data they allege was withheld was material.

Sandoz's Response:

In light of the above paragraphs, Sandoz asks the Court to find that the withheld data and information were material.

(ii) Dr. Pinchasi Had An Intent to Deceive the PTO

668. Defendants have proffered no direct evidence that Dr. Pinchasi had an intent to deceive the PTO, and they have failed to introduce any evidence from which an inference of an intent to deceive could be drawn.

Sandoz's Response:

Sandoz provides specific objections to Teva's arguments below.

669. On the contrary, Dr. Pinchasi's testimony established that she believed and believes to this day that there is a correlation between the average molecular weight of copolymer-1 compositions and their potential to cause toxicity in the RBL degranulation assay and the *in vivo* mouse toxicity assay, and that the data in Example 2 accurately reflects this correlation. (July Tr. (Pinchasi) 135:6-22.) The Court credits Dr. Pinchasi's testimony, and her testimony is corroborated by her contemporaneous documents.

Sandoz's Response:

For the reasons stated above, Dr. Pinchasi's belief in a correlation between molecular weight and toxicity does not excuse her intentional cherry-picking of data to improve the arguments in support of patentability. For the reasons stated above and in Sandoz's opening brief, Dr. Pinchasi was not a credible witness.

670. Circumstantial evidence also supports the conclusion that Dr. Pinchasi acted in good faith. Had Dr. Pinchasi deliberately sought to conceal from the PTO examiner the fact that high molecular weight batches could show low toxicity, as Defendants contend, the very first page of the '037 application would not reference and incorporate Dr. Bornstein's 1987 article, which describes copolymer-1 compositions with average molecular weights of about 14,000 to 23,000 daltons as inducing less than 30% degranulation. (PTX 31 at 408-09.)

Sandoz's Response:

The circumstantial and direct evidence shows that Teva made different representations regarding the Bornstein BR-1 studies, depending on the audience. Dr. Pinchasi testified that the FDA told Teva "that if the BR-1 study will prove to be in line with their definition of one of the pivotal studies, which is everything that I described before, yes, they will accept it as one of the BR-1 [sic: pivotal] studies" (July Tr. 37:2-14.) [redacted]

[redacted]

[redacted]. While Teva listed the Bornstein article in the Background of the Invention, Teva never provided a copy of the Bornstein paper until 10 years into the prosecution of the patents and after seven of the nine patents had already issued. (PTX 20 at TEV000304847.) Neither Dr. Pinchasi nor Teva told the PTO that the molecular weight values in Bornstein were lower than reported to the *New England Journal of Medicine*. The circumstantial evidence on this issue favors a finding of Dr. Pinchasi having an intent to deceive the PTO.

671. The evidence also showed that Dr. Pinchasi lacked any motive to intentionally deceive the PTO. As Dr. Pinchasi credibly testified, the copolymer-1 project did not hinge on getting patent protection for Copaxone®. Teva entered into the project, and continued to develop the product, with the expectation that it would not have such protection. (July Tr. (Pinchasi) 19:23-22:3, 117:22-118:8, 295:12-17; PTX 41A.)

Sandoz's Response:

See Sandoz's Responses to Teva's Proposed FOF Nos. 639-47 for evidence of Dr. Pinchasi's motive, which is not an element of an inequitable conduct defense.

672. Dr. Pinchasi also did not provide any contradictory or inconsistent information to the PTO and the FDA regarding the toxicity and safety of the claimed low average molecular weight copolymer-1 compositions. as compared to those used in the Bornstein clinical trial, since safety and tolerability are different concepts. Moreover, intent cannot be inferred when Teva disclosed numerous references containing substantially the same substantive information as was provided to the FDA during prosecution of the patents. *Rothman v. Target Corp.*, 556 F.3d 1310, 1328 (Fed. Cir. 2009) (submission of letters discussing two prior art styles negates any

inference of an intentional deception in failure to submit same prior art).

Sandoz's Response:

Teva provides no citation for the "numerous references containing substantially the same substantive information as was provided to the FDA during prosecution of the patents." Teva did not present a single piece of evidence to the PTO showing the toxicity of any batch of copolymer-1 between 8.4 and 13 kDa, despite having the data readily available and in the patent file the night it filed its patent application; nor did it disclose its lack of confidence in the RBL test.

673. Thus, Defendants have failed to prove clearly and convincingly that Dr. Pinchasi intended to deceive the PTO.

Sandoz's Response:

Sandoz submits that it has proven by clear and convincing evidence that Dr. Irit Pinchasi engaged in inequitable conduct during the prosecution of the patents-in-suit.

674. As Defendants have failed to prove either materiality or intent to deceive by clear and convincing evidence, their inequitable conduct defense must be dismissed.

Sandoz's Response:

Sandoz submits that it has proven materiality and intent by clear and convincing evidence, and the Court should find that Dr. Irit Pinchasi engaged in inequitable conduct during the prosecution of the patents-in-suit.

X. FINDINGS OF FACT AND CONCLUSIONS OF LAW RELATING TO DEFENDANTS' OBVIOUSNESS DEFENSE

675. Defendants also argue that the claims-in-suit would have been obvious to a person of ordinary skill in the art as of May 24, 1994, the filing date of the '037 application. In making this argument, Defendants focus on two categories of limitations in the asserted claims. First, Defendants argue that copolymer-1 falling within the claimed average molecular weight ranges, or having the claimed molecular weight distribution, would have been obvious. Second, Defendants argue that certain process limitations for making copolymer-1 – in particular the use of HBr in acetic acid to achieve the desired molecular weight – would have been obvious. Defendants have failed, however, to focus on the claims as a whole, as is required to establish

obviousness. Even limiting the analysis to the limitations for which Defendants presented evidence, Defendants have failed to present clear and convincing evidence that either the molecular weight or process limitations of the claims of the patents-in-suit would have been obvious to a person of ordinary skill in the art as of May 24, 1994.

Sandoz's Response:

Sandoz will respond in more detail below, but notes that the invention of the patents-in-suit was described as an "improvement" over the inventors' own prior art. It was entirely appropriate to focus Sandoz's obviousness defense on the claimed "improvements."

A. Legal Principles

676. To succeed on their obviousness claims, Defendants must prove by clear and convincing evidence that "the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103; *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006). The clear and convincing standard is a heightened standard of proof, and a defendant raising an invalidity defense bears "a heavy burden of persuasion." *Microsoft Corp.*, *131 S. Ct.* at 2246-47. "When, as here, a party asserts invalidity of a patent and bases that assertion on evidence, including prior art references, that was before the patent examiner when he allowed the patent claims, the difficulty of overcoming the presumption of validity is greater than it would be if the evidence relied on was not before the examiner." *In re Omeprazole Patent Litigation*, 490 F. Supp. 2d at 500 (citing *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d at 1358-60 (Fed. Cir. 1984)). "In determining whether to allow the application, the patent examiner is also presumed to have considered each reference that was before him individually and in combination with every other reference before him." *Astra Aktiebolag v. Andrx Pharmaceuticals, Inc.*, 222 F. Supp. 2d 423, 562 (S.D.N.Y. 2002), *aff'd sub nom*, *In re Omeprazole Patent Litig.*, 84 Fed. Appx. 76 (Fed. Cir. 2003) ; *see also Microsoft Corp.*, 131 S. Ct. at 2250.

677. To determine whether a claim is obvious, the Court must consider: "(1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) evidence of secondary factors, also known as objective indicia of nonobviousness." *Eisai Co. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1356 (Fed. Cir. 2008) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). The first three factors comprise the so-called *prima facie* case of obviousness. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1350 (Fed. Cir. 2000).

Sandoz's Response:

This is a misleading statement of law. "*Prima facie* obviousness" refers to the procedural allocation of burdens when considering obviousness. *See generally*, M.P.E.P. § 2142 ("Legal Concept of Prima Facie Obviousness"). While one can establish *prima facie* obviousness by

proving each of the three so-called *Graham v. John Deere* factors cited by Teva, it is not the only way to establish a *prima facie* case. As set forth in more detail below and in Sandoz's Proposed Finding of Facts and Conclusions of Law, claims drawn to ranges of properties are *prima facie* obvious if they "overlap or lie inside ranges disclosed by the prior art." *See generally*, M.P.E.P. § 2144.05.

678. The obviousness analysis requires an examination of the subject matter as a whole to ascertain if the claimed invention would have been obvious at the time that invention was made. 35 U.S.C. § 103; *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 401, 406 (2007). To the extent the claimed invention contains elements described in the prior art, the patent challenger must "identify[] 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.'" *Takeda Chem. Indus, Ltd.. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (quoting *KSR Int'l Co.*, 550 U.S. at 401). "Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Id.* at 1357. This is the best protection against the subtle but powerful attraction of a hindsight-based obviousness analysis. *See Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1363 (Fed. Cir. 2009).

Sandoz's Response:

For reasons explained in more detail below, Teva is misstating the holding in *Takeda*, a case regarding the making of a new chemical compound. The facts of this case do not trigger any legal requirements for Sandoz to prove a "motivation to combine" or "reason that would have prompted" someone to make the claimed invention. This is a point of legal disagreement between Sandoz and Teva. The point is likely moot, however, because the evidence supports a finding of the "motivation" and "reason" Teva claims is required under the law.

The Supreme Court in *KSR* eliminated "motivation to combine" as a required element of an obviousness analysis. *See generally*, *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238-45 (Fed. Cir. 2010) (discussing *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007).) Teva cites *Takeda Chem. Indus, Ltd.. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007) for the proposition that, despite the Supreme Court's decision in *KSR*, motivation to combine is a

required element of proof when the subject matter of the invention is a new chemical compound. *Takeda* is inapplicable here. According to the inventors of the patents-in-suit, copolymer-1 batches of varying molecular weights are not different chemical compositions. For example, Drs. Teitelbaum, Arnon, and Sela described copolymer-1 batches of varying molecular weights above and below the range of between 17 kDa and 50 kDa as "[m]olecules of identical composition," but having different molecular weights. (PTX 509 at 1172.)

The patents-in-suit describe a mere "improvement" in copolymer-1. (PTX 1, 808 patent, col. 1:1 (listing title as "Copolymer-1 improvements in compositions of copolymers"); *id.* at 1:38-39 ("It is an object of the present invention to provide an improved composition of copolymer-1."). As the patents describe, lower molecular weight embodiments can be isolated from one another using chromatographic separation. (PTX 1, '808 patent, col. 2:53-col. 3:2. The various batches that are isolated are all still called copolymer-1. They are not "new chemical compounds." Thus, cases like *Takeda* do not apply here. *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007) ("[I]n cases involving *new chemical compounds*, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.") (emphasis added).

679. As the Federal Circuit Court of Appeals has recently reiterated, the danger of improper hindsight is most visible when the patent challenger selects claim elements from the prior art without providing any reason that the person of ordinary skill in the art would combine them at all, let alone in the manner recited by the claim. *In re NTP, Inc.*, No. 2010-1243, 2011 U.S. App. LEXIS 15814, at *39-40 (Fed. Cir. Aug. 1, 2011). "Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'" *Id.* at *39-40 (quoting *Grain Processing Corp. v. American-Maize Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988)).

Sandoz's Response:

Sandoz's obviousness defense does not use the patents-in-suit as a guide to show that the patents-in-suit are obvious. Rather, Sandoz compares the prior art to the patents-in-suit and proves that the differences between the two would have been obvious to one of skill in the art.

680. Where the prior art discredits, disparages or somehow leads a person of skill in the art away from the claimed invention, that prior art is said to "teach away" from the invention and, thus, establish nonobviousness. *E.g.*, *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009); *Spectralytics, Inc. v. Cordis Corp.*, No. 2009-1564, 2011 WL 2307402, at *4-5 (Fed. Cir. June 13, 2011). What a reference teaches, and whether it teaches toward or away from the claimed invention, is a question of fact addressed to a person of skill in the art. *Spectralytics, Inc. v. Cordis Corp.*, 2011 U.S. App. LEXIS 11981, at *15.

681. If a *prima facie* case of obviousness has been demonstrated, the patentee may offer evidence of secondary considerations of nonobviousness to rebut that showing. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1305 (Fed. Cir. 2010). Such evidence, when present, must be considered and includes the extent of commercial success of the patented invention, unexpected properties of the invention, whether the invention satisfies a long-felt need, whether others have failed to find a solution to a problem addressed by the patent, and any copying of the invention by others. *See Transocean Offshore Deepwater Drilling, Inc.*, 617 F.3d at 1304-5; *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006). The ultimate burden of proof on obviousness is always with the patent challenger and "never shifts." *See Tech. Licensing Corp. v. Videotek. Inc.*, 545 F.3d 1316, 1329 (Fed. Cir. 2008).

B. Findings of Fact

(i) Scope and Content of Prior Art Regarding Copolymer-1 and the Molecular Weight Characteristics of Copolymer-1

682. As described above in paragraphs 134-140, Professor Ruth Arnon and her colleagues at the Weizmann Institute discovered copolymer-1 in the 1960s, and first published their research on copolymer-1 in the 1971 Teitelbaum article. Because copolymer-1 was modeled after myelin basic protein, Pros. Arnon and her colleagues aimed for an average molecular weight of about 23,000 daltons. July Tr. (Arnon) 309:21-311:8. The 1971 Teitelbaum article described copolymer-1 as having an average molecular weight of 23,000 daltons. (July Tr. (Arnon) 311:24-312:22; PTX 499 at 242.)

683. In September 1974, Professor Arnon and her colleagues at the Weizmann Institute published an abstract reporting that copolymer-1 had been found to suppress EAE, a biological model for MS. (PTX 509 at 1172.) The abstract states that copolymer-1 has a molecular weight of 23,000 daltons. (PTX 509 at 1172.) The abstract further reports that copolymer-1 compositions with molecular weights lower than 17,000 daltons or higher than 50,000 daltons "proved ineffective for the treatment of EAE." (July Tr. (Arnon) 312:23-313:18; Sept. Tr.

(Grant) 1442:8-1444:9; PTX 509 at 1172-1173.)

Sandoz's Response:

Sandoz notes that the 1974 abstract was later discredited to the extent Teva argues that the 1974 reference "taught away" from using a copolymer-1 composition for the suppression of EAE or the treatment of multiple sclerosis. The 1987 Bornstein article taught the public that copolymer-1 with a molecular weight as low as 14,000 daltons was effective at treating multiple sclerosis. (*E.g.*, PTX 31 at 408, 413 ("Cop 1 is a random polymer (molecular weight 14,000 to 23,000). . . . This pilot trial examined the effects of Cop 1 on a selected sample of patients with actively exacerbating multiple sclerosis. . . . The results show that Cop 1, administered subcutaneously for two years at a daily dose of 20 mg, produced clinically important and statistically significant beneficial effects . . . .").)

684. The '550 patent, which issued to Yeda on November 19, 1974, describes compositions of several copolymers, including copolymer-1. The '550 patent states that the disclosed copolymers generally have a molecular weight "in excess of 10,000, and preferably above about 18,000" daltons. (Sept. Tr. (Grant) 1435:4-1437:19; Sept. Tr. (Zeiger) 839:18-840:18; PTX 26, col. 1:57-68.)

Sandoz's Response:

Sandoz does not dispute the selected facts regarding the '550 patent, but notes that by focusing on the date it was issued, Teva gives the impression that the '550 patent came three years after the 1971 Teitelbaum article. The 1971 Teitelbaum article was published in March 1971. (PTX 499 at 248.) The '550 patent claims priority to a patent application filed in April 1971 by the same authors as the 1971 Teitelbaum article – Drs. Teitelbaum, Arnon, and Sela. The three later went on to be named inventors of the patents-in-suit. (PTX 26, '550 patent, col. 1:3-8; PTX 1-9.) The '550 patent cites 1971 Teitelbaum on its face. (PTX 26, '550 patent, col. 4:31.) It cites to no other journal articles. The Court should find:

SDZ369. One of skill in the art reading the ’550 patent would consider the 1971 Teitelbaum article to provide additional insight into the teachings of the ’550 patent.

685. The only specific disclosure of copolymer-1 in the specification of the ’550 patent appears in column 2, lines 19-30 of the patent specification. (Sept. Tr. (Grant) 1435:4-1437:19; Sept. Tr. (Zeiger) 933:14-934:18; PTX 26, col. 2:19-30.) There, the ’550 patent describes a preferred copolymer, which is copolymer-1, having “a molecular weight of about 20,000 to 25,000” daltons. (Sept. Tr. (Grant) 1436:17-1437:9; Sept. Tr. (Zeiger) 933:21-934:4; PTX 26, col. 2:19-30.)

Sandoz’s Response:

To the extent Teva is trying to argue that the ’550 patent does not disclose copolymer-1 with a minimum molecular weight of 10 kDa, Sandoz has fully briefed this issue and noted that Teva repeatedly admitted during the prosecution of the patents-in-suit that the ’550 patent discloses such a copolymer-1 composition. (Sandoz’s Opening FFCOL ¶¶ 30-32, 318-322.) Teva should be estopped from arguing otherwise here.

686. All of the claims of the ’550 patent are directed to copolymers, including copolymer-1, having a molecular weight of 15,000 to 25,000 daltons. (Sept. Tr. (Grant) 1437:10-19; Sept. Tr. (Zeiger) 840:25-841:6; PTX 962 (B. Rao 6/9/2010 Dep.) at 103:5-105:13, 196:10-197:10, 198:9-199:12; PTX 26, col. 3:24 – col. 4:23; PTX 320 at MYL0000616.)

Sandoz’s Response:

While the claims are directed to copolymer-1 having a molecular weight between 15 and 25 kDa, the specification described copolymers with molecular weights as low as “being in excess of 10,000 and preferably above about 18,000.” (PTX 26 (’550 Patent, Col. 1:57-65).)

687. The ’550 patent does not state how the average molecular weights reported in the patent were determined or the methodology used to generate the measurement. (Sept. Tr. (Grant) 1434:13-16, 1438:2-7; Sept. Tr. (Zeiger) 939:6-19, 956:10-957:13, 958:23-959:3.) The ’550 patent contains no disclosure, teaching or data regarding the molecular weight distribution or molar fractions of any copolymer. (Sept. Tr. (Grant) 1434:13-16, 1438:16-19; 1439:7-24, 1441:1-25; Sept. Tr. (Zeiger) 956:10-18, 957:2-6; PTX 26; PTX 320 at MYL0000616.)

Sandoz's Response:

Sandoz fully briefed its argument that one of ordinary skill in the art would read the contemporaneous 1971 Teitelbaum paper and understand that the molecular weights described in the '550 patent were determined by ultracentrifugation using a Spinco model E ultracentrifuge, which provided a weight average molecular weight. (Sandoz's Opening FFCOL ¶¶ 26-29.) Dr. Scandella testified to that fact without any contradiction. (*Id.*) Teva's citations in the proposed finding point to testimony that the method of determining molecular weight is not within the four corners of the '550 patent itself. However, Dr. Grant admitted that the 1971 Teitelbaum article obtained its molecular weight values by use of ultracentrifugation. (Sept. Tr. 1440:3-25.) To the extent Dr. Grant believes that the March 1971 Teitelbaum article should not be considered hand-in-hand with the '550 patent, file in April 1971, the Court should credit Dr. Scandella's testimony over Dr. Grant's.

688. During the prosecution of the '808 patent, the examiner rejected then-pending claims 17-20 as *prima facie* obvious in view of the '550 patent. (*See* PTX 13 at TEV000304138-144.) The applicants were able to overcome the obviousness rejection over the '550 patent by arguing that the '550 patent did not raise a *prima facie* case of obviousness, *i.e.*, by pointing out to the examiner that the '550 patent did not teach or suggest the claimed invention. (PTX 13 at TEV000304151-152.) The applicants did not rely on secondary considerations or unexpected results to overcome the obviousness rejection based on the '550 patent. (*See* PTX 13 at TEV000304151-152, 162-167).

Sandoz's Response:

The requirements for patentability are that an invention be new, useful, and not obvious. 35 U.S.C. §§ 101-103. To overcome the above obviousness rejection, Teva did not merely argue that its invention was not *prima facie* obvious. Rather, it argued that its invention, unlike the '550 patent, did not "suggest any advantage to obtaining particular molecular weight fractions of copolymer-1 through the claimed method." (PTX 13 at TEV000304151.) By pointing to the

"advantage," Teva was arguing that its invention was useful, new, or not obvious. By pointing to an "advantage," Teva was arguing unexpected results compared to the '550 patent.

Even if the argument to the "advantage" of its invention was not a reference to unexpected results, the PTO should have required unexpected results because Teva's arguments did not otherwise overcome the obviousness rejection. Indeed, when the Examiner was considering the exact same claim in product form (product claim 1 of the '589 is the product version of method claim 1 of the '808 patent), the Examiner acknowledged that "applicants have, however, demonstrated unexpected results for copolymers having lower molecular weights in the instant working examples." (PTX 14 at TEV000309024.) While the Examiner's remarks were in a paragraph discussing the EP '620 patent application, the reasoning applied equally to the '550 patent.

689. The examiners of each of the other eight patents-in-suit considered the '550 patent extensively during prosecution of the patents-in-suit. (*See, e.g.,* PTX 14 at TEV000309018; PTX 15 at TEV000309103; PTX 17 at TEV000304221; PTX 18 at TEV000310385; PTX 19 at TEV000304453; PTX 20 at TEV000304582; PTX 21 at TEV000308838.) After the prosecution of the '808 patent, there were no subsequent obviousness rejections raised based on the '550 patent. (*See* PTX 13-21.)

<u>*Sandoz's Response:*</u>

After the first two obviousness rejections based on the '550 patent, (PTX 12 at TEV000309546; PTX 13 at TEV000304142), the Examiner made several anticipation rejections over the '550 patent. (E.g., PTX 15 at TEV000309109; PTX 17 at TEV000304219; PTX 18 at TEV000310336; PTX 19 at TEV000304448-49.) The Examiner also rejected the claims over the '550 patent based on the doctrine of "obviousness-type double-patenting." (PTX 19 at TEV000304509-10 ("Claims 19-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of USP 5,891,589 taken in view of Teitelbaum et al (USP 3,849,550).)

While most of these rejections were for anticipation, such rejections are implicitly obviousness rejections, too. "[A] disclosure that anticipates under § 102 also renders the claim invalid under § 103, for 'anticipation is the epitome of obviousness.'" *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (*quoting In re Fracalossi*, 681 F.2d 792 (C.C.P.A. 1982)). Despite having its claims rejected as anticipated, Teva made "unexpected results" arguments to overcome those rejections. (*See* Sandoz's Opening FFCOL ¶ 322 and accompanying chart.) But unexpected results cannot overcome anticipation rejections as a matter of law. (*See* M.P.E.P. § 2131.04 ("Evidence of secondary considerations, such as unexpected results or commercial success, is irrelevant to 35 U.S.C. § 102 rejections and thus cannot overcome a rejection so based.") (*citing In re Wiggins*, 488 F.2d 538, 543 (C.C.P.A. 1973).) "Unexpected results" are relevant to overcoming *prima facie* obviousness rejections, however. *See, e.g., Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007) (holding that patent owner "failed to show unexpected results that would tend to rebut a prima facie case of obviousness"); *In re Merck & Co.*, 800 F.2d 1091, 1098 (Fed. Cir. 1986) ("A *prima facie* case of obviousness can be rebutted by evidence of unexpected results.") Teva was "anticipating" its obviousness rejections and beating the Examiner to the punch. Because the "unexpected results" arguments were accepted at the same time Teva's anticipation arguments were accepted, the Examiners did not have to issue separate obviousness rejections after Teva overcame its anticipation rejections.

690. European Patent Application No. 0383620 ("the EP '620 Application"), filed by Repligen Corporation on February 16, 1990 and published on August 22, 1990, discloses a biological process for making genes encoding polypeptides involving the use of recombinant DNA technology. (Sept. Tr. (Grant) 1445:4-22, 1446:23-1447:14; Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 11, ll. 32-34.) The process described in the EP '620 Application does not involve the chemical synthesis of N-carboxyanhydrides. (Sept. Tr. (Grant) 1445:4-22, 1446:23-1447:14; Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 2, ll. 50-55.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

691. The EP '620 Application states that the process described can be used to make individual polypeptides that are "similar to" copolymer-1. (Sept. Tr. (Zeiger) 884:23-885:4, 972:15-20; DTX 1970, p. 2, l. 50.) These individual polypeptides are not mixtures like copolymer-1, and thus they do not have average molecular weights. Instead, each individual polypeptide disclosed has a discrete molecular weight. (Sept. Tr. (Grant) 1445:8-1446:4, 1446:23-1448:16; Sept. Tr. (Zeiger) 975:9-23, 976:15-23, 977:17-978:3; DTX 1970, p. 2, ll. 50-55, p. 11, ll. 32-34.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

692. The EP '620 Application discloses that the molecular weight of each individual polypeptide could be in the range of 5,000 to 50,000 daltons, but the reference focuses on individual polypeptides with sizes between 15,000 and 23,000 daltons because "COP-1 polypeptides within this range were previously tested in chemical trials." (Sept. Tr. (Grant) 1448:20-1449:19; Sept. Tr. (Zeiger) 977:8-978:3; DTX 1970, p. 5, 1l. 28-33.) Thus, the reference to 5,000 and 50,000 daltons in the EP '620 Application are references to individual molecular weights, not average molecular weights. (Sept. Tr. (Zeiger) 975:14-976:23.) The EP '620 Application does not disclose any copolymers having an "average molecular weight" of 5,000 daltons. (Sept. Trial (Grant) 1447:15-1448:10; Sept. Trial (Zeiger) 977:17-20.) Further, the EP '620 Application does not disclose measuring the average molecular weight of any copolymer using size exclusion chromatography, *i.e.*, using an appropriately calibrated suitable gel filtration column. (Sept. Trial (Grant) 1448:11-13; Sept. Trial (Zeiger) 976:15-23.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

693. The EP '620 Application contains no disclosure or teaching regarding a molecular weight distribution or molar fractions of copolymer-1. (Sept. Tr. (Grant) at 1448:17-19; *see generally* DTX 1970.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

694. The Examiners of all nine patents-in-suit also considered the EP '620 Application. (*See e.g.,* PTX 13 at TEV000304110; PTX 14 at TEV000309018; PTX 15 at TEV000309103; PTX 17 at TEV000304221; PTX 18 at TEV000310385; PTX 19 at TEV000304453; PTX 20 at TEV000304582; PTX 21 at TEV000308838.) During prosecution of the patents-in-suit, the applicants were able to overcome any obviousness rejections based on the EP '620 Application for any allowed claims without relying on evidence of unexpected results, and the Examiners of

the patents-in-suit never cited unexpected results as the sole reason for allowing any claim over the EP ’620 Application.

Sandoz’s Response:

Sandoz adopts Mylan’s response to this proposed finding of fact.

695. The precise reason for copolymer-1’s biological activity remains unknown. (Sept. Tr. (Lisak) 118:3-8.) Whether certain portions of copolymer-1 or certain peptides found within copolymer-1 are responsible for its therapeutic properties also is not known. (DTX 1970 at 2:25.) Copolymer-1 batches with molecular weight distributions that overlap do not necessarily have the same function or activity in biological assays. (Sept. Tr. (Grant) 1460:14-1462:5, DTX 1762 at TEV003017837.)

Sandoz’s Response:

The reason for copolymer-1’s biological activity is unknown whether one is considering copolymer-1 in the context of the 1971 Teitelbaum article (PTX 499), the ’550 patent (PTX 26), the 1987 Bornstein paper (PTX 31), or the patents-in-suit (PTX 1-9). Both the prior art and the patents-in-suit copolymer-1 compositions are effective at treating multiple sclerosis. (E.g., PTX 31 at 413 (“This pilot trial examined the effects of Cop 1 on a selected sample of patients with actively exacerbating multiple sclerosis. . . . The results show that Cop 1, administered subcutaneously for two years at a daily dose of 20 mg, produced clinically important and statistically significant beneficial effects . . . .”); PTX 1, ’808 patent, col. 1:51-53 (“[T]he invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.”) The inventors of the patents-in-suit did not claim to discover why copolymer-1 has therapeutic properties. Accordingly, the uncertainty of how copolymer-1 works does nothing to distinguish the patents-in-suit from the prior art.

696. Dr. Zeiger testified regarding the obviousness of the copolymer-1 molecular weight characteristics claimed in the patents-in-suit. Dr. Zeiger admitted, however, that he has never measured the molecular weight of a copolymer using SEC. (Sept. Tr. (Zeiger) 928:25-929:2.) In that same vein, Dr. Zeiger testified that he is aware that the Court has construed “average molecular weight” to mean “peak molecular weight detected using an appropriately calibrated suitable gel filtration column.” (Sept. Tr. (Zeiger) 940:15-23.) But Dr. Zeiger testified that he does not hold himself out as an expert in SEC with respect to the use of

molecular weight calibrants. (Sept. Tr. (Zeiger) 929:20-25.)

Sandoz's Response:

None of the inventors of the patents-in-suit had ever measured the molecular weight of a copolymer using SEC. The Weizmann inventors (Arnon, Sela, Teitelbaum) only had access to an ultracentrifuge. (July Tr. 276:19-277:3 (Pinchasi); 343:4-345:9 (Arnon).) [redacted] If the inventors of the patent-in-suit had never used SEC to measure copolymer-1, the Court should not make experience measuring copolymer-1 with SEC a prerequisite to testifying about obviousness.

697. Dr. Zeiger likewise offered testimony regarding the obviousness of the claim limitations directed to the molecular weight distribution of copolymer-1, *i.e.*, the molar fraction claim limitations. But at his deposition, Dr. Zeiger could not recall ever generating a molecular weight distribution curve. (Sept. Tr. (Zeiger) 929:3-11, 953:6-11.)

Sandoz's Response:

None of the inventors of the patents-in-suit had generated a molecular weight distribution curve. [redacted] The Court should not make experience generating molecular weight curves a prerequisite to testifying about obviousness.

698. Dr. Zeiger's opinions on these issues are entitled to little weight. Dr. Zeiger has never done any research regarding the fundamental underpinnings of SEC (Sept. Tr. (Zeiger) 929:15-17), and was not, in fact, proffered by the Defendants as an expert in SEC (Sept. Tr. (Zeiger) 798:4-800:16.).

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

699. Dr. Zeiger also offered the opinion that the claims directed to the treatment of multiple sclerosis (*e.g.*, claim 23 of the '539 patent) would have been obvious over the prior art. (PTX 8.) The Court should not credit these opinions, as Dr. Zeiger is not qualified to offer them. Dr. Zeiger admitted that he is not a medical doctor and that he has no experience treating people with multiple sclerosis. (Sept. Tr. (Zeiger) 966:7-16.) Despite his expertise being in biochemistry and polymer chemistry, Dr. Zeiger testified that he is confident that it would have been obvious to treat people with a new copolymer-1 composition. (Sept. Tr. (Zeiger) 967:16-22.)

Sandoz's Response:

This is irrelevant because no expert testimony was required to understand in 1994 that using copolymer-1 to treat multiple sclerosis was obvious in light of the prior art. Anyone could pick up the *New England Journal of Medicine* in 1987 and read that Dr. Bornstein successfully treated patients suffering from multiple sclerosis by administering copolymer-1. (PTX 31 at 408.) Even the much earlier '550 patent recognized copolymer-1 as a "treatment or prevention of certain autoimmune diseases affecting the brain" such as experimental allergic encephalomyelitis ("EAE"), which, according to the patent, "serves as a model disease for multiple sclerosis. . . ." (PTX 26, '550 patent, col. 1:14-16; 28-30.)

(ii) Scope and Content of Prior Art Regarding Debenzylation Using HBr/acetic Acid

700. The patentees discovered and described in the patents-in-suit that the HBr in acetic acid used during the debenzylation stage in the process for making copolymer-1 would cleave the polypeptides formed during polymerization and, thus, could also be used to control the average molecular weight of the resulting copolymer-1. (Sept. Tr. (Sampson) 1641:8-23.) The patentees also discovered that by varying the time and temperature of the debenzylation reaction using HBr in acetic acid, a copolymer-1 composition with a predetermined molecular weight profile, such as 7,000 daltons, could be synthesized. (Sept. Tr. (Sampson) 1641:18-1642:8; PTX 1, col. 4:48-col. 6:3.) Defendants have failed to show that these discoveries would have been obvious.

Sandoz's Response:

Sandoz disputes that the patentees made any "discovery" with respect to the use of HBr in acetic acid with copolymer-1, as discussed in further detail below, and in Sandoz's opening Findings of Fact and Conclusions of Law. (*See* Sandoz's Opening FFCOL ¶ 191.) Sandoz also adopts Mylan's response to this proposed finding of fact, and further notes that Defendants have met their burden to show that the asserted claims that encompass the use of HBr in acetic acid in manufacturing copolymer-1 would have been obvious.

701. As Dr. Sampson testified, a person of skill in the art would not have been motivated to use HBr in acetic acid to cleave the peptide bonds in copolymer-1 polypeptides in order to control the molecular weight of a copolymer-1 sample. On the contrary, the prior art as a whole taught that peptide bonds would not be cleaved during exposure to HBr/acetic acid. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1689:22-1690:11.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

Teva's description of Dr. Sampson's testimony is incomplete. Dr. Sampson agreed with Dr. Laird that multiple publications available prior to 1994 would have allowed a person of skill in the art to conclude that use of HBr in acetic acid resulted in peptide bond cleavage. (Sept. Tr. 1663:25-1664:10, 1666:12-19 (referring to DTX 3329), 1666:20-1667:21, (referring to DTX 3327), 1668:19-1669:9 (referring to DTX 1781), 1670:2-20 (referring to DTX 1783).) Dr. Laird testified that it was well known at the time of the invention to use HBr in acetic acid to cleave peptide bonds. (Sept. Tr. 1138:16-22, 1139:10-21, 1140:9-1141:16, 1143:1-1144:11, 1147:7-1148:9.).

702. As Dr. Sampson explained, HBr/acetic acid was a standard deprotecting agent used during the *synthesis* of polypeptides. In those cases, cleavage of the polypeptide chain would need to be minimized or avoided altogether. One of ordinary skill attempting to make polypeptides would not have been motivated to use a reagent that would *break* polypeptides. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1655:13-1656:4; PTX 488.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

Furthermore, Dr. Laird testified that if a person of skill in the art wanted to make copolymer-1 of a lower molecular weight they would have been motivated to use HBr in acetic acid as it had previously been used in manufacturing copolymer-1, and they would have expected it to partially cleave the peptide bonds. (Sept. Tr. 1143:14 – 1144:11; 1155:13 -23.)

703. Dr. Sampson explained that of all the prior art references discussed at trial, only three directly investigated whether peptide bond cleavage occurred as a result of the use of HBr/acetic acid. Each of these references concluded that no cleavage had occurred. (Sept. Trial Tr. (Sampson) 1650:7-1651:9.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

In addition to Dr. Zeiger's testimony, Dr. Sampson testified that multiple publications available prior to 1994 would have allowed a person of skill in the art to conclude that use of HBr in acetic acid resulted in peptide bond cleavage. (Sept. Tr. 1663:25-1664:10, 1666:12-19 (referring to DTX 3329), 1666:20-1667:21, (referring to DTX 3327), 1668:19-1669:9 (referring to DTX 1781), 1670:2-20 (referring to DTX 1783).) Dr. Laird also testified that it was well known at the time of the invention to use HBr in acetic acid to cleave peptide bonds. (Sept. Tr. 1138:16-22, 1139:10-21, 1140:9-1141:16, 1143:1-1144:11, 1147:7-1148:9.)

704. A 1963 paper by nobel laureate Bruce Merrifield, "Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide," *J. Am. Chem. Soc.*, 85: 2149-54 (1963) ("Merrifield 1963") (PTX 488), one of the most widely cited papers in peptide chemistry, taught that peptide bond cleavage would not occur upon exposure to HBr/acetic acid. (Sept. Trial Tr. (Sampson) 1644:10-1647:10; PTX 488.) Significantly, Dr. Merrifield specifically investigated whether peptide cleavage had taken place after treatment with HBr/acetic acid for 18 hours at 25°C, conditions similar to those described in the patents-in-suit. He found no cleavage. (Sept. Trial Tr. (Sampson) 1644:20-1647:10; PTX 488 at 2151, 2153.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

In addition, an excerpt from a 1965 textbook entitled "The Peptides" sent from W.R. Grace to Dr. Varkony at Teva in 1988, post-dates the Merrifield article. (DTX1269 at TEV03017895; Sept. Tr. 1671:12-24 (Sampson).). Dr. Sampson testified that this 1965 book states that peptide bonds have a "tendency to cleavage" and "are in danger of being cleaved" upon treatment with HBr in acetic acid. (Sept. Tr. 1671:22-1673:7; DTX 1269 at TEV003017896 states "It is worthwhile noting that the considerable amounts of the diester are formed on treatment of L-glutamic acid α-benzyl ester with hydrogen bromide in glacial acetic acid. Peptide bonds are also in danger of being cleaved"; DTX 1269 at TEV003017898 states that peptide bonds have a "tendency to cleavage" when using HBr in acetic acid as a cleaving reagent under a standard condition.)

Dr. Varkony was an original inventor on the '037 application. (PTX 11 at TEV000309434.) Despite knowing of a prior art reference showing that HBr in acetic acid cleaves peptides, neither Teva nor Dr. Varkony disclosed this reference to the PTO during prosecution of the patents-in-suit.

705. Similarly, Yaron & Berger, "Multi-Chain Polyamino Acids Containing Glutamic Acid, Aspartic Acid and Proline," *Biochimica et Biophysica Acta*, 107: 307-332 (1965) ("Yaron & Berger 1965") (DTX 1934) reported that no cleavage of peptide bonds was detected when HB/acetic acid was used for debenzylation carried out at 2 degrees for 3 days. (Sept. Trial Tr. (Sampson) 1650:7-1651:9; Sept. Trial Tr. (Zeiger) 851:9-853:3; 1685:13-22; PTX 1934.) The authors reported that under those conditions, they were able to obtain 100 percent deprotection of benzyl groups and avoid peptide bond cleavage. (Sept. Trial Tr. (Sampson) 1650:7-1651:9; 1685:13-22; Sept. Trial Tr. (Zeiger) 851:9-853:20; PTX 1934.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

706. Yaron and Berger, "Multichain Polyamino Acids of Well Defined Degrees of Polymerization, *Bulletin of the Research Counsel of Israel: Section A, Chemistry*, 7A(2):96-97 (1958) ("Yaron & Berger 1958") (DTX 3233) also investigated whether peptide bond cleavage occurred when HBr in acetic acid was used to deprotect benzyl groups during the synthesis of copolymers. The authors concluded that "no degradation in the side chains occurred during

debenzylation with HBr in glacial acetic acid at 2 degrees for three days." (Sept. Trial Tr. (Sampson) 1650:7-1651:9; Sept. Trial Tr. (Laird) 1146:9-1147:6.) As Dr. Sampson explained, this meant that no peptide bonds had been cleaved even after three days of exposure to HBr/acetic acid.

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

707. According to both Dr. Sampson and Sandoz's expert Dr. Laird, the time and temperature of 2 degrees for three days reported in Yaron and Berger 1958 would be equivalent, through the application of a well-known chemical rule of thumb to about 22-25 degrees for about 17-18 hours, conditions similar to those reported in the patents-in-suit. (Sept. Trial Tr. (Laird) 1146:9-1147:6; Sept. Trial Tr. (Sampson) 1650:7-1651:9, 1685:13-1686:18; PTX 1934 at 318; PTX 3233 at 97.) Since *no cleavage* was observed in the conditions used in Yaron and Berger 1958, one of ordinary skill in the art in 1994 would similarly expect that use of HBr in acetic acid for 17 hours at 25°C, as described in Example 4 of the patents-in-suit, would likewise result in *no cleavage* of peptide bonds. (Sept. Trial Tr. (Sampson) 1685:13-1686:18; DTX 1934 at 318.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

708. The other prior art references discussed by Drs. Zeiger and Laird would not teach the person of ordinary skill to use HBr/acetic acid to cleave peptide bonds.

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

Dr. Sampson, and Dr. Laird each testified that multiple references would teach a person of ordinary skill to use HBr/acetic acid to cleave peptide bonds. Dr. Sampson testified that multiple publications available prior to 1994 would have allowed a person of skill in the art to conclude that use of HBr in acetic acid resulted in peptide bond cleavage. (Sept. Tr. 1663:25-1664:10, 1666:12-19 (referring to DTX 3329), 1666:20-1667:21, (referring to DTX 3327), 1668:19-1669:9 (referring to DTX 1781), 1670:2-20 (referring to DTX 1783).) Dr. Trevor Laird also testified that it was well known at the time of the invention to use HBr in acetic acid to

cleave peptide bonds. (Sept. Tr. 1138:16-22, 1139:10-21, 1140:9-1141:16, 1143:1-1144:11, 1147:7-1148:9.)

709. The two prior art references that mention the use of HBr/acetic acid during the synthesis of copolymer-1, the ’550 patent and the 1971 Teitelbaum article, describe using HBr/acetic acid only for the purpose of debenzylation – *i.e.*, removing the benzyl protecting group from the glutamic acid in protected copolymer-1. (Sept. Trial Tr. (Sampson) 1651:20-1652:11, 1653:4-1655:12; PTX 26, col. 2:53-64; PTX 499 at 243.) Neither of these references mention peptide bond cleavage during the debenzylation step, nor do they mention the use of HBr in acetic acid to control the molecular weight of the resulting copolymer-1 product. (Sept. Trial Tr. (Sampson) 1651:20-1652:11, 1653:4-1655:12; PTX 26; PTX 499.)

Sandoz’s Response:

Sandoz adopts Mylan’s response to this proposed finding of fact.

Furthermore, Dr. Laird testified that if a person of skill in the art wanted to make copolymer-1 of a lower molecular weight they would have been motivated to use HBr in acetic acid as it had previously been used in manufacturing copolymer-1, and it would have expected to partially cleave the peptide bonds. (Sept. Tr. 1143:14 – 1144:11.)

710. Dr. Sampson testified that a person of ordinary skill in the art would have understood that the Weizmann scientists controlled molecular weight by adjusting the ratio of initiator to N-carboxyanhydrides of the respective amino acids during polymerization. (Sept. Trial Tr. (Sampson) 1652:12-1656:4; PTX 499; DTX 1783.)

Sandoz’s Response:

Sandoz adopts Mylan’s response to this proposed finding of fact.

711. Two of the prior art references relied on by the Defendants – the Katchalski & Sela reference and the Hayashi reference – discuss the use of HBr for debenzylation purposes in compounds other than copolymer-1, but they contain no independent or original observations concerning peptide bond cleavage. These references simply report discussion of suspected bond cleavage from earlier literature (Sept. Trial Tr. (Sampson) 1647:11-1648:10), and neither mentions the use of HBr/acetic acid to control molecular weight. (*See* Sept. Trial (Sampson) 1647:25-1648:10, 1653:10-1655:8; Sept. Trial (Zeiger) 820:17-821:4; DTX 1781; DTX 1783.) Moreover, Hayashi 1985 does not even discuss the use of HBr in acetic acid. (Sept. Trial (Laird) 1150:16-1151:12; DTX 1781 at 464.)

Sandoz’s Response:

Sandoz adopts Mylan’s response to this proposed finding of fact.

712. Four other prior art references relied on by the Defendants discuss possible peptide bond cleavage based upon an observed change in the molecular weight of a peptide after the use of HBr. These references, however, contain no direct observation or testing to determine whether, in fact, peptide bond cleavage had occurred and whether HBr was responsible for such cleavage. (*See* Sept. Trial Tr. (Sampson) 1648:11-1650:6; DTX 1855; DTX 3327; DTX 1784.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

713. As Dr. Sampson testified, it is also significant that the references Defendants' experts rely that suggest possible peptide bond cleavage all pre-date the Merrifield article. A person of skill in the art in 1994 looking at the literature as a whole, including the Merrifield article, would not have understood that HBr in acetic acid would cleave peptide bonds. The person of ordinary skill in the art would therefore not have been motivated to use that reagent in order to control the molecular weight of copolymer-1. (Sept. Trial Tr. (Sampson) 1655:13-1656:17.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

In addition to the two references relied upon by Dr. Zeiger that post-date Merrifield (DTX 1934 and DTX 1784), Dr. Sampson testified that the 1965 book entitled "The Peptides" post-dates the Merrifield article, and states that peptide bonds have a "tendency to cleavage" and "are in danger of being cleaved" upon treatment with HBr in acetic acid. (Sept. Tr. 1671:22-1673:7; DTX 1269 at TEV003017896 and TEV003017898.) Dr. Sampson also testified that multiple publications available prior to 1994 would have allowed a person of skill in the art to conclude that use of HBr in acetic acid resulted in peptide bond cleavage. (Sept. Tr. 1663:25-1664:10, 1666:12-19 (referring to DTX 3329), 1666:20-1667:21, (referring to DTX 3327), 1668:19-1669:9 (referring to DTX 1781), 1670:2-20 (referring to DTX 1783).)

714. This finding is supported by the fact that Defendants' experts could not point to a single literature reference in all the years prior to 1994 that actually used HBr/acetic acid to control the molecular weight of a polypeptide. (Sept. Tr. (Sampson) 1689:22-1690:11.)

Sandoz's Response:

Sandoz adopts Mylan's response to this proposed finding of fact.

(iii) Facts Relating to Secondary Conditions

715. MS was first recognized as a distinct disease in the 1860s. (Sept. Tr. (Lisak) 88:8-89:18.) Yet by the early 1990s, despite repeated attempts by multiple entities, no effective treatment had been developed that could slow the progress of the disease. (Sept. Tr. (Lisak) 102:2-9, 131:14-136:19; PTX 523; PTX 538; PTX 565; PTX 591.) In 1994, the only disease-modifying treatment available for MS was Betaseron®, an interferon treatment that is ineffective in about 40% of MS patients and that causes significant side effects, including liver and bone marrow problems, depression, and a flu-like syndrome. (Sept. Tr. (Lisak) 125:25-126:3, 103:3-104:2, 104:11-105:18.) Thus, in 1994, there remained unmet needs for (1) another effective treatment for RRMS patients; (2) a RRMS treatment that worked differently than an interferon treatment; and (3) an effective treatment that was more tolerable and caused less side effects than an interferon treatment. (Sept. Tr. (Lisak) 126:10-127:18; Sept. Tr. (Green) 1392:11-1393:20.)

Sandoz's Response:

Dr. Bornstein's patients were effectively treated for MS with copolymer-1 in the 1980s. (PTX 31.) Betaseron (an interferon) was launched in the United States in July 1993 – one year before Teva applied for the patents-in-suit. (Sept. Tr. 46:23-47:1 (Congleton); Lisak Slide 9.) Teva says that in 1994, there was an "unmet" need for the invention. Teva does not say that there was a "long-felt, but unmet" need, which is the correct legal standard. *See Graham v. John Deere Co*, 383 U.S. 1 (1966) (listing secondary considerations including "long felt but unsolved needs"). By 1994, copolymer-1 was already proven by Dr. Bornstein to be an effective treatment for MS. (PTX 31 at 413.) The demand for something other than Betaseron was not "long felt," as Betaseron had only been on the market ten months when Teva filed its patent. (Sept. Tr. 46:23-47:1 (Congleton); Lisak Slide 9.) By the time Copaxone came to the market, other MS drugs, such as Avonex had entered the market. (*Id.* (noting that Avonex entered the market in 1996).)

716. The introduction of Copaxone® in 1997 fulfilled all of these needs. (Sept. Tr. (Lisak) 127:15-130:25; PTX 667; PTX 671. Copaxone® works differently than interferons and is thus able to effectively treat many of the patients for whom interferons are ineffective. (Sept. Tr. (Lisak) 103:3-104:2, 118:9-119:7; 127:15-130:25; PTX 667, PTX 671.) Copaxone® also does not cause many of the significant side effects associated with interferon therapy. (Sept. Tr. (Lisak) 117:1-15.) With Copaxone®, physicians were able to provide an effective treatment option for patients that did not respond to the interferons, and that did not cause the significant

side effects associated with interferon treatment. (Sept. Tr. (Lisak) 126:12-127:20.) While Mylan's clinician expert, Dr. Green, opined that the higher molecular weight copolymer-1 studied by Dr. Bornstein in the 1980s would have satisfied these needs if it had been approved, this speculative testimony is not reliable given that Dr. Green was not even practicing medicine until 2001—well after the time period relevant to this secondary consideration. (Sept. Tr. (Green) 1364:19-24; 1380:3-19.)

Sandoz's Response:

Copaxone in 1997 was no better than the copolymer-1 used by Dr. Bornstein in the 1980s. Both were effective treatments for MS. (PTX 31 at 413.) Teva relied on Bornstein's clinical trials to support its application for Copaxone. (*See* Sandoz FFCOL ¶¶ 193-197.)

While Copaxone works differently than interferons, the "demand" for something that works differently than interferons had only been in existence for less than one year. One year is not a long-felt need.

717. Dr. Lisak explained that his prescriptions for Copaxone® have increased over time because of the clinical advantages of the product over the competing treatments. (Sept. Tr. (Lisak) 119:8-120:9.) Dr. Lisak's testimony is consistent with the observation of Teva's corporate representative, Mr. Jon Congleton that as physicians gained experience prescribing Copaxone®, "they saw the benefit that their patients were deriving" and "[a]s that knowledge accumulated, that experience accumulated, the utilization of Copaxone grew." (Sept. Tr. (Congleton) 50:12-51:2.)

Sandoz's Response:

Sandoz does not dispute that Copaxone is a successful drug. However, being a successful drug has no relevance to whether it was obvious in 1994 in light of the fact that copolymer-1 had already been shown to be an effective treatment for multiple sclerosis years earlier in clinical trials.

718. The undisputed facts demonstrate that Copaxone®, Teva's copolymer-1 treatment for RRMS, has been a substantial commercial success. Annual sales of Copaxone® have grown nearly 100-fold from $25 million in 1997 to approximately $2.25 billion in 2010. (Sept. Tr. (Congleton) 49:8-12, 59:18-20.) Sales of Copaxone® in the United States have steadily grown and overtaken sales of its interferon competitors during this time and it has become the treatment of choice for RRMS by nearly a factor of two. (Sept. Tr. (Congleton) 50:12-51:2.) Since its introduction, total sales for Copaxone® have exceeded $10 billion, despite constant pressure from competitors. (Sept. Tr. (Congleton) 59:21-23, 66:6-7.) Approximately 100,000 patients are

currently using Copaxone® to treat their multiple sclerosis. (Sept. Tr. (Congleton) 51:19-22.)

Sandoz's Response:

Sandoz does not dispute that Teva has sold a lot of Copaxone for a very high price. But to be a "commercial success" in the context of secondary considerations of obviousness, there must be a nexus between the claimed features of the patented invention and its commercial success. *See. e.g., Muniauction Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 (Fed. Cir. 2008). Teva claims that its invention is distinguishable over the copolymer-1 used in the Bornstein studies because it has a lower molecular weight. But Dr. Greene testified, without contradiction, that there are no clinically significant differences between Bornstein's copolymer-1 and Teva's Copaxone. (Sept. Tr. 1370:17-21.) Other Teva witnesses also admitted there was no evidence of a difference in side effects between the Bornstein and Johnson studies. (*E.g.*, July Tr. 265:18-267:1 (Pinchasi).) Thus, Teva failed to show that Copaxone's commercial success in comparison to the prior art was attributable to its lower molecular weight.

719. Natco and Mylan also represented in their ANDA submission to the FDA that Copaxone® is the "first choice of drug for remitting relapsing form of multiple sclerosis." (PTX 320 at MYL0000615.) "When compared to other disease[] modifying drugs . . ., glatiramer acetate has fewer side effects. It is also [the] drug of choice for patients of multiple sclerosis to be shifted from Interferon beta 1a and 1b due to adverse reactions and intolerance." (PTX 320 at MYL0000615; *see also* PTX 963 (B. Rao 9/30/2010 Dep.) at 226:23-228:13 (testifying that Copaxone® has "a better side-effect profile" and "a better therapeutic efficacy profile" as compared to the interferon treatments).)

Sandoz's Response:

Everything that Natco and Mylan said in the above paragraph would also be true of the copolymer-1 used by Dr. Bornstein in the 1980s.

720. The evidence at trial demonstrated that Copaxone® and Teva's process for manufacturing Copaxone® are covered by at least one claim of each of the patents-in-suit. (Sept. Tr. (Gokel) 1589:13-1590:20.) Dr. Gokel testified at trial that Copaxone® meets the "copolymer-1" term, as it has been construed by the Court. (Sept. Tr. (Gokel) 1588:15-1589:12, 530:25-531:25.) Dr. Gokel further explained that Teva uses the same process steps that are in the patents-in-suit to make Copaxone®. (Sept. Tr. (Gokel) 1584:9-1590:20.)

Sandoz's Response:

Sandoz does not dispute that Dr. Gokel gave conclusory testimony that Copaxone is covered by the claims of the patents-in-suit. Whether Copaxone is covered by the claims of the patents-in-suit will depend, in part, on whether the Court accepts Teva's broad interpretation of the 6:2:5:1 molar ratio claim limitations. Sandoz maintains that its proposed product does not meet the 6:2:5:1 limitation. If Sandoz does not meet that limitation, the Court may also conclude that Copaxone is not within the claim scope, either.

721. Dr. Grant testified that based on the data he had seen from Copaxone® certificates analysis and calculations based on data provided by Sandoz and Mylan that Copaxone® meets the average molecular weight, copolymer-1 molar fraction and TFA-copolymer-1 limitations of the asserted claims. (PTX 105, PTX 349 at SDZ00017948-949; PTX 392 ; PTX 990 at "Copolymer-1 Molar Fraction Limitations-Copaxone" and "TFA Copolymer-1 Molar Fraction Values-Copaxone"; Sept. Tr. (Grant) 1468:5-1477:15.)

Sandoz's Response:

Sandoz does not dispute that Dr. Grant gave conclusory testimony that Copaxone is covered by the claims of the patents-in-suit.

722. Dr. Lisak's testimony at trial also demonstrates that Copaxone® meets the limitations related to treatment of multiple sclerosis. (Sept. Tr. (Lisak) 137:4-147:22; Sept. Tr. (Gokel) 1589; PTX 206; PTX 697; PTX 734.)

Sandoz's Response:

Sandoz does not dispute that Dr. Lisak testified that Copaxone treats multiple sclerosis.

723. The evidence at trial also established that Copaxone® is covered by at least one claim of each of the patents-in-suit. Dr. Grant, testified that Copaxone® meets the average molecular weight and molar fraction limitations of each claim of the patents-in-suit. (Sept. Tr. (Grant) 1476:25-1477:15.) Dr. Gokel also testified that at least one claim of each patent-in-suit covers Copaxone®. (Sept. Tr. (Gokel) 531:4-25, 1584:9-1590:20.**)**

Sandoz's Response:

Sandoz does not dispute that Drs. Grant and Gokel gave conclusory testimony that Copaxone is covered by at least one claim of each of the patents-in-suit. Dr. Grant said that

Copaxone meets "the average molecular weight" limitations of the patents-in-suit, without specifying a particular claim or any particular average molecular weight limitation. Dr. Gokel's testimony regarding whether Copaxone is covered by 8 of the 9 patents-in-suit (PTX 2-9) is reproduced in its entirety:

> Q. Now, sir, in your binder we have the remaining asserted patents Exhibits 2 through 9 and I don't want to run through those in detail, but have you conducted a similar analysis to consider whether Copaxone and the process for making Copaxone meet at least one asserted claim of each of those asserted patents, PTX 2 through 9?
>
> A. Yes, I have made such an analysis.
>
> Q. And what is your opinion, sir?
>
> A. It's my opinion that at least one claim in each of the asserted patents is met by Copaxone.
>
> Q. Thank you. I want to move on . . .

(Sept. Tr. 1590:11-21 (Gokel).) The Court should not adopt Teva's proposed finding based on such conclusory testimony.

724. The success of Copaxone® has occurred in a difficult drug development environment. Since the 1860s, numerous attempts to develop an effective treatment for MS have failed. (Sept. Tr. (Lisak) 131:14-132:7.) Despite showing some promise, these treatments have failed to either benefit the patient, were toxic or not tolerated, and in some cases, actually worsened the disease. (Sept. Tr. (Lisak) 131:14-136:19.)

Sandoz's Response:

The success of using copolymer-1 to treat multiple sclerosis in humans began as early as the 1980s with Dr. Bornstein's treatment of patients in his clinical trials. (PTX 31 at 408.) Teva does not contend that Bornstein's work was a failure. It cannot. Teva relied on the success of the Bornstein trial to support its NDA for Copaxone. (Sandoz FOF ¶ 186, 193-97.)

725. At trial, Dr. Lisak described some of the more recent failed attempts to develop MS treatments. Isoprinisone and prednisone were both tested in the early 1980s and found not to provide any benefit in slowing the progression of the disease. (PTX 523; Sept. Tr. (Lisak)

132:18-24.) Transfer factors, obtained from the white blood cells of healthy individuals, were also studied but found not to provide any benefit to MS patients. (Sept. Tr. (Lisak) 132:18-24; PTX 538.)

Sandoz's Response:

None of these other attempts to make an MS drug are relevant. Dr. Bornstein tried to use copolymer-1 as a treatment for multiple sclerosis and succeeded. The failures cited by Teva were not directed to copolymer-1, let alone copolymer-1 with lower toxicity as compared to the copolymer-1 taught by Bornstein 1987.

726. Various immunosuppressants have also failed as effective treatments for MS. Trials on Roquinimex were cut short due to the discovery of significant side effects, including heart attacks and even deaths in some patients. (Sept. Tr. (Lisak) 132:25-133:4; PTX 627.) Gusperimus failed to provide any benefit to patients. (Sept. Tr. (Lisak) 133:5-7; PTX 591.) Sulfasalazine failed to show any therapeutic benefit after three years of patient use, even though the drug initially looked promising after a year of use. (Sept. Tr. (Lisak) 133:7-12; PTX 617.) Cladribine is a chemotherapy drug that turned out to have unacceptable toxicity for use in treating MS. (Sept. Tr. (Lisak) 133:15-21; PTX 644.)

Sandoz's Response:

None of these other attempts to make an MS drug are relevant. Dr. Bornstein tried to use copolymer-1 as a treatment for multiple sclerosis and succeeded. The failures cited by Teva were not directed to copolymer-1, let alone copolymer-1 with lower toxicity as compared to the copolymer-1 taught by Bornstein 1987.

727. Lenercept, a cytokine modulator used to treat rheumatoid arthritis, was tested for efficacy in treating MS and not only failed to provide any benefit, some patients endured more attacks of MS symptoms and developed more active lesions. (Sept. Tr. (Lisak) 133:23-134:6; PTX 623.) Infliximab, another cytokine modulator, was also ineffective in treating MS and worsened the condition of some patients. (Sept. Tr. (Lisak) 134:7-10; PTX 605.) TGF-β2 is a cytokine that was shown to provide no therapeutic benefits in clinical trials. (Sept. Tr. (Lisak) 134:11-14; PTX 616.)

Sandoz's Response:

None of these other attempts to make an MS drug are relevant. Dr. Bornstein tried to use copolymer-1 as a treatment for multiple sclerosis and succeeded. The failures cited by Teva

were not directed to copolymer-1, let alone copolymer-1 with lower toxicity as compared to the copolymer-1 taught by Bornstein 1987.

728. Several antigen-derived therapies have also failed as effective treatments for MS. Patients who received oral bovine myelin in Phase III clinical studies fared no better than patients on placebo. (Sept. Tr. (Lisak) 134:15-21; PTX 644.) Tiplimotide, another antigen therapy, actually worsened the condition of some patients. (Sept. Tr. (Lisak) 134:22-25; PTX 626.)

Sandoz's Response:

None of these other attempts to make an MS drug are relevant. Dr. Bornstein tried to use copolymer-1 as a treatment for multiple sclerosis and succeeded. The failures cited by Teva were not directed to copolymer-1, let alone copolymer-1 with lower "toxicity" than the copolymer-1 taught by Bornstein 1987.

729. Despite some promise, various monoclonal antibodies have also failed as treatments for MS. Muromonab-CD3 is a monoclonal antibody that cause significant toxicity in patients. (Sept. Tr. (Lisak) 135:3-8; PTX 565.) Priliximab was found to be ineffective in a Phase II clinical study. (Sept. Tr. (Lisak) 135:3-8; PTX 644.) Development of Antova for treatment of autoimmune diseases, including MS, stopped after patients began developing blood clots and deep vein thrombosis. (Sept. Tr. (Lisak) 135:9-13; PTX 99.)

Sandoz's Response:

None of these other attempts to make an MS drug are relevant. Dr. Bornstein tried to use copolymer-1 as a treatment for multiple sclerosis and succeeded. The failures cited by Teva were not directed to copolymer-1, let alone copolymer-1 with lower "toxicity" than the copolymer-1 taught by Bornstein 1987.

730. As referenced above in paragraphs 165-69, the record also reflects that the lower molecular weight copolymer-1 developed by the inventors achieved unexpected results, including reduced toxicity. Further, the record shows that both defendants copied the synthetic process for making copolymer-1 claimed in the patents-in-suit. *See* Paragraphs 288-300, 252-257.

Sandoz's Response:

Sandoz incorporates its responses to paragraphs 165-169, 252-257, and 288-300. To the extent that Teva claims it achieved unexpected results with its invention, it misled the PTO regarding those results, which were accepted by the PTO as a basis for allowing the claims. Regarding copying, the record does not support the allegation. Moreover, Teva's allegations of copying are irrelevant because Sandoz no longer does what Teva alleges was copied from its patents. (*See* Sandoz's Responses to ¶¶ 23, 300.)

C. Conclusions of Law

(i) Copolymer-1 Compositions Having the Claimed Average Molecular Weight Characteristics Were Obvious.

731. Defendants rely on two pieces of prior art in support of their contention that the claimed copolymer-1 compositions would have been obvious to the person of ordinary skill in the art: U.S. Patent 3,849,550 ("the '550 patent") and the EP '620 Application ("EP '620 Application"). As set forth above, the PTO considered both the '550 patent and the EP '620 Application during the prosecution of each of the nine patents-in-suit. Therefore, Defendants face a heavy burden of proving invalidity. *In re Omeprazole Patent Litigation*, 490 F. Supp. 2d at 500 (citing *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1358-60 (Fed. Cir. 1984)); *see also Tokai Corp.*, 632 F.3d at 1367.

Sandoz's Response:

Teva ignores the full basis of Sandoz's obviousness defense. Sandoz also relies on the 1987 Bornstein article (PTX 31) (or the 1991 Bornstein article) to support its obviousness argument. (See Dckt. No. 272 (Sandoz's Statement of Claims and Defenses) at 3 ("The asserted claims are rendered obvious by U.S. Patent No. 3,849,550, Murray B. Bornstein et al., 317 *New Eng. J. Med.* 408 (1987), and/or Murray B. Bornstein et al., 41 *Neurology* 533 (1991).").)

732. Neither the '550 patent nor the EP '620 Application, alone, in combination, or in view of the knowledge of the person of ordinary skill in the art renders obvious copolymer-1 compositions with the claimed average molecular weight ranges.

Sandoz's Response:

The '550 patent alone or in combination with the 1987 Bornstein paper renders the claims of the patents-in-suit *prima facie* obvious, which shifts the burden to Teva to come forward with evidence of nonobviousness. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007). Reliance on the EP '620 Application is not necessary to invalidate the patent. Sandoz has no disagreement with Mylan regarding the defenses based on the EP '620 Application. Mylan simply presents additional evidence to invalidate the claims.

733. The '550 patent does not disclose a copolymer-1 composition having an average molecular weight of about 5,000 to 9,000 daltons or within any of the other claimed molecular weight ranges, nor does it suggest such a composition. (Sept. Tr. (Zeiger) 841:19-842:13.) Indeed, Mylan's expert, Dr. Zeiger, admitted that the '550 patent teaches that the preferred molecular weight range for the copolymers it discloses is above 18,000 daltons. (Sept. Tr. (Zeiger) 840:16-18, 843:1-3.) Like the '550 patent, the EP '620 Application does not disclose copolymer-1 compositions with an average molecular weight of about 5,000 to about 9,000 daltons. Indeed, the EP '620 Application is not even directed to copolymer-1 compositions, as the term "copolymer-1" has been interpreted by the Court. (Sept. Tr. (Grant) 1445:4--1447:-14; Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 2, ll. 50-55, p. 11, 1.32-1.34.) Instead, the EP '620 Application is directed to discrete polypeptides made through recombinant DNA technology and identifies a preferred molecular weight for these individual polypeptides of 15,000 to 23,000 daltons. (Sept. Tr. (Grant) 1448:20-1449:19; Sept. Tr. (Zeiger) 972:15-20, 977:8-978:3; DTX 1970, p. 5, 1l. 28-33.)

Sandoz's Response:

The '550 patent describes copolymer-1 with an average molecular weight in the range of 10,000 to 25,000 daltons. (Sandoz FOF ¶¶ 183-192.) This molecular weight range abuts or overlaps the ranges of molecular weights described in the '808, '589, '847, '539, '430, '476,'161, and '098 patents. (Sandoz FOF ¶ 213.) Both the '550 patent and the patents-in-suit were directed to the same chemical composition – copolymer-1. (*E.g.*, PTX 1, '808 patent, col. 1: 32-44 ("Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine . . . . The present invention relates to a composition of copolymer-1 . . . ."); PTX 26, '550 patent, col. 2:19-22 ("A preferred copolymer according to the present invention

comprises in combination alanine, glutamic acid, lysine and tyrosine. . . .”).) Because the patent claims have the same chemical composition as the ’550 patent, and because the patent claims are expressed in ranges falling within and/or adjacent to the range recited in the ’550 patent, the claims are *prima facie* obvious. *See In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955); *In re Hill*, 284 F.2d 955, 959 (C.C.P.A. 1960).

Sandoz has asked the Court to reconsider its claim construction ruling of the “average molecular weight” terms to exclude any copolymer-1 composition with a weight average molecular weight in excess of 10,000 daltons. (*See* Sandoz’s Opening FFCOL ¶¶ 24-29 and accompanying claim construction brief.) If the Court adopts Sandoz’s proposed claim construction, the molecular weight range of the ’550 patent will only abut the claim ranges of the patents-in-suit. It will not overlap. To the extent that the Court does not revise its claim construction to exclude copolymer-1 compositions with a weight average molecular weight greater than 10 kDa, then the ranges will necessarily overlap, too.

734. Defendants have offered no reason why, based on the prior art, the person of ordinary skill in the art would have been motivated to make a copolymer-1 composition with a peak average molecular weight of about 5,000 to 9,000 daltons. *Takeda Chem. Indus.*, 492 F.3d at 1350 (“[i]t remains necessary to identify some reason that would have lead a chemist to modify a known compound in a particular manner to established prima facie obviousness of a new claimed compound”). Nothing in the prior art suggests any reason that a person of ordinary skill would change, adjust or lower the average molecular weight of copolymer-1 to the claimed ranges. Based on the teachings of the ’550 patent and the EP ’620 Application, the person of ordinary skill in the art would have no reason to select or to make a copolymer-1 composition in the specific average molecular weight range of about 5 to 9 kilodaltons, or within the ranges of “about 4 to about 9 kilodaltons,” or 6.25-8.4 kilodaltons.

Sandoz’s Response:

There is clear and convincing evidence of motivation. Teva claims that its invention is an improved copolymer-1 because it lowered the molecular weight and reduced toxicity. Dr. Rice testified, as a toxicologist who was experienced working with polymers, that it was known that

changing various parameters, including molecular weight, can affect toxicity. (Sept. Tr. 1015:4-10; 1047:8-13.)

Although Sandoz presented evidence of motivation, such evidence was not required. Teva misstates the law regarding motivation to combine and its applicability to this case. The Supreme Court in *KSR* eliminated "motivation to combine" as a required element of an obviousness analysis. *See generally*, *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238-45 (Fed. Cir. 2010) (discussing *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007).) Teva cites *Takeda Chem. Indus, Ltd.. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007) for the proposition that, despite the Supreme Court's decision in *KSR*, "[i]t remains necessary to identify some reason that would have lead a chemist to modify a known compound in a particular manner to established prima facie obviousness of a new claimed compound." Teva's above citation delete the beginning of the *Takeda's* holding, which states in its entirety, "Thus, *in cases involving new chemical compounds*, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chem,* 492 F.3d at 1357 (emphasis added). This case involves the same chemical compound fractionated or cleaved to a different average molecular weight, not a "new chemical compound."

According to the inventors of the patents-in-suit, copolymer-1 batches of varying molecular weights are not different chemical compositions. For example, Drs. Teitelbaum, Arnon, and Sela describe copolymer-1 batches of varying molecular weights above and below the range of between 17 kDa and 50 kDa as "[m]olecules of identical composition," but having different molecular weights. (PTX 509 at 1172.) The patents-in-suit describe a mere "improvement" in copolymer-1. (PTX 1, 808 patent, col. 1:1 (listing title as "Copolymer-1

improvements in compositions of copolymers"); *id.* at 1:40-41 ("It is an object of the present invention to provide an improved composition of copolymer-1."). As the patents describe, lower molecular weight embodiments can be isolated from one another using chromatographic separation. (PTX 1, '808 patent, col. 2:53-col. 3:2. The various batches that are isolated are all still copolymer-1. They are not "new chemical compounds."

735. In fact, the prior art would have taught the person of ordinary skill *away* from making a copolymer-1 composition with an average molecular weight of about 5,000 to about 9,000 daltons. Both the '550 patent and the EP '620 Application express a preference for compositions with molecular weights above 15,000, and more preferably between 20,000 and 25,000 daltons. (Sept. Tr. (Grant) 1437:10-19; 1448:20-1449:19; Sept. Tr. (Zeiger) 933:21-934:4, 977:8-978:3; PTX 26, col. 3:24-col. 4:3; DTX 1970, p. 5, 1l. 28-33.) By teaching that higher average molecular weights were preferred, these references teach away from the claimed lower average molecular weight copolymer-1 compositions. *See e.g., Takeda Chem. Indus.*, 492 F.3d at 1357-58**;** *In re Baird*, 16 F.3d 380, 382-83 (Fed. Cir. 1994)**.**

Sandoz's Response:

Teva ignores the 1987 Bornstein paper as a basis for Sandoz's obviousness defense. The '550 patent issued in 1974. (PTX 26.) It states a preference for using copolymer-1 with an average molecular weight between 20-25 kDa, but it does state why 20-25 kDa is preferred or that there is anything unacceptable about the 10 kDa copolymer-1 embodiment disclosed in the '550 patent. By 1987, Bornstein publicly stated that his copolymer-1 had a molecular weight of 14-23 kDa. (PTX 31 at 408.) One of skill in the art reading the Bornstein paper would have observed that the preferred molecular weight range of copolymer-1 had decreased since 1974 through the 1994 filing date of the patents-in-suit.

Dr. Rice testified that that it is known that changing various parameters, including molecular weight, can affect toxicity. (Sept. Tr. 1015:4-10; 1047:8-13.) Nothing in the '550 patent or the 1987 Bornstein paper instructs those of skill in the art not to try even lower molecular weights of copolymer-1. When taking into consideration that the Bornstein 1987 paper is a weight average molecular weight, whereas the claims of the patent in suit are

expressed as a peak molecular weight (according to the Court's claim construction), to the extent there is any gap between the molecular weight in 1987 Bornstein and the claims of the patents-in-suit, the gap is *deminimus*. [redacted] Teva claims that its patents cover copolymer-1 with average molecular weights as high as 9,900 daltons. (Sept. Tr. 1486:1-21 (Grant).). Nothing in the 1987 Bornstein paper suggests that the copolymer-1 would be any less effective if the molecular weight were lowered. (PTX 31.)

736. This is entirely consistent with the teaching of other available prior art, like the 1974 Teitelbaum reference, which expressly teaches away from copolymer-1 with an average molecular weight below 17,000 daltons, identifying such a composition as "ineffective" for the treatment of EAE." (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:9; PTX 509 at 1172-1173.)

Sandoz's Response:

The 1974 Teitelbaum abstract (PTX 509) was authored by the Drs. Teitelbaum, Arnon, and Sela. (PTX 509 at 1172.) The 1987 Bornstein paper was likewise co-authored by Drs. Teitelbaum, Arnon, and Sela, along with Dr. Bornstein, thirteen years later. (PTX 31.) The 1987 Bornstein paper stated that copolymer-1 with a molecular weight as low as 14,000 daltons was effective at treating patients with MS. In light of this finding, one of ordinary skill in the art in 1994 would not credit the older 1974 abstract and still conclude that copolymer-1 below 17,000 daltons was ineffective. Moreover, the 1974 Teitelbaum abstract discusses treating EAE, whereas the 1987 Bornstein paper describes actually successfully treating humans suffering from MS. (PTX 509; PTX 31.) While EAE is a model for treating MS, one of skill in the art would not credit the 1974 Teitelbaum abstract's EAE results over the 1987 Bornstein results when trying to develop "a pharmaceutical composition and a method for the treatment of multiple sclerosis. . . ." (PTX 1, '808 patent, col. 1:51-53.)

737. Apparently acknowledging that they have provided no evidence as to why a person of ordinary skill in the art would have lowered the average molecular weight of copolymer-1 based upon the prior art, Defendants argued at trial that *prima facie* obviousness can be established based solely on what they describe as overlapping or abutting molecular weight ranges between the copolymer-1 compositions of the prior art and the claimed copolymer-1 compositions. Defendants' argument does not hold up when applied to the case law concerning overlapping or abutting ranges.

Sandoz's Response:

For the reasons explained above and below, Sandoz established a *prima facie* case of obviousness at trial.

738. First, there is no overlapping or abutting range with respect to the claimed "average molecular weight." Even if the '550 patent taught a copolymer-1 composition having an "average molecular weight," *i.e.*, a peak molecular weight detected using an appropriately calibrated suitable gel filtration column, of 10,000 daltons (which it does not), such a composition does not overlap with a peak average molecular weight range of "about 5 to 9 kilodaltons," "about 4 to about 9 kilodaltons" or "6.25-8.4 kilodaltons." (Sept. Tr. (Zeiger) 938:11-15; 941:8-16.)

Sandoz's Response:

There is substantial evidence that there is overlapping or abutting molecular weight ranges in the patents-in-suit and the prior art based on the testimony of Drs. Rice and Zeiger and based on a comparison of the claims of the patents-in-suit to the '550 patent. (*See* Sandoz FOF ¶¶ 212-227.)

739. Nor does the peak average molecular weight of "about 9 kilodaltons" "abut" an average molecular weight of 10,000 daltons. In order to abut, prior art and claimed ranges must literally touch. *See e.g., In re Woodruff*, 919 F.2d 1575, 1576, 1578 (disclosed range of "about 5%" abutted claimed range of "more than 5%"); *In re Malagari*, 499 F.2d 1297, 1298, 1303 (C.C.P.A. 1974) (disclosed range of 0.03 and 0.07% carbon abutted range of 0.02-0.03%). Here, the '550 patent does not disclose how the molecular weights of the disclosed copolymers were measured, but even if it discloses a peak average molecular weight of 10 kilodaltons, the "average molecular weight" ranges of the claims and the '550 patent do not touch. Nor can an overlapping or "abutting" range case be made out with regard to the EP '620 Application, which discloses neither copolymer-1 nor an average molecular weight for copolymer-1. (Sept. Tr. (Grant) 1444:13-1448:16; Sept Tr. (Zeiger) 884:23-885:4, 972:15-20, 975:9-23, 976:15-23; DTX 1970, p.2, l. 50.)

<u>*Sandoz's Response:*</u>

Teva's statement of the law is misleading. Teva claims that in order to "abut," the "prior art and claimed ranges must literally touch." But the law does not require strict "abutting." A *prima facie* case of obviousness is established even if the ranges do not literally abut if the ranges are close and one skilled in the art would expect them to have the same properties. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985) (finding claims prima facie obvious when claimed ranges were "so close" that one of skill in the art would expect them to have the same properties); *see generally*, M.P.E.P. § 2144.05 ("[A] a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties.").

Teva's characterization of the facts is also wrong. The '550 patent's minimum molecular weight of 10 kDa is not a peak molecular weight. (Sandoz's Opening FFCOL ¶¶ 26-29.) For the reasons stated above, one of ordinary skill in the art would understand that the '550 patent discloses a minimum weight average molecular weight of 10 kDa. (*Id.*) Its peak molecular weight would, therefore, be *less than* 10 kDa. (*Id.* ¶ 216.) Even if the '550 patent were considered to have a peak molecular weight of 10 kDa, the claims of the patents-in-suit would abut that value, too. (*Id.* ¶ 221.)

740. Rather than address the invention as claimed, Defendants argue that because there must have been an overlap in the molecular weight of some of the species within the mixture of copolymer-1 batches alleged to be in the prior art with the distributions of the claimed invention, there is an overlap in the claimed ranges. This is incorrect as a matter of law and science. As a matter of law, the "overlapping range" cases refer to an overlap of ***claimed*** ranges. *See e.g.*, *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("A prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.") Here, Defendants acknowledge that they have not demonstrated such an "overlap." (Sept. Tr. (Zeiger) 941:8-16.)

Sandoz's Response:

The range of copolymer-1 molecular weights disclosed in the '550 patent abut or are sufficiently close to the molecular weight ranges of the patents-in-suit to establish a *prima facie* case of obviousness. (Sandoz FOF ¶¶213-216, 221-227.) To the extent that the Court does not construe the claims of the patents-in-suit to exclude copolymer-1 with a weight average molecular weight of greater than 10 kDa, the claimed ranges also overlap, particularly with regard to the "75% between 2 to 20 kDa" limitations in the '430, '476, '161, and '847 patents. The '550 patent describes copolymer-1 in the range of 10 kDa to 25 kDa. (PTX 31, '550 patent, col. 1:59-62, col. 3:25:28.) Some copolymer-1 compositions with greater than 10 kDa weight average molecular weights having 75% of their molar fraction between 2 and 20 kDa will have a weight average molecular weight within the '550 patent's range of 10 to 25 kDa, for example, copolymer-1 compositions composed of copolymer-1 fractions with molecular weights between 10 and 20 kDa.

Teva's misinterprets Dr. Zeiger's testimony regarding the overlap in peak molecular weights. Teva's counsel asked Dr. Zeiger several transcript pages worth of questions about the '808 patent, which has an average molecular weight range of "about 5 to 9 kDa." (Sept. Tr. 939:23-944:10). Throughout that questioning, Zeiger Slide 19 was on the Court's screen, which was entitled "U.S. Patent No. 5,800,808." (*Id.*; Zeiger Slide 19.) Within a series of questions relating to the '808 patent, Teva's counsel asked one question about the "asserted claims in the patents in suit," which Teva now interprets in isolation to mean all of the asserted claims of all of the patents. The transcript reflect that Dr. Zeiger was testifying about the '808 patent at the time. The claims of the "having 75% of its molar fraction within the molecular weight range from

about 2 kDa to about 20 kDa" claims in the '430, '476, '161, and '847 overlap with the '550 patent's 10 to 25 kDa claim range, as explained above.

741. Moreover, defendants have *no* prior art to rely on to establish this alleged "overlap." Instead, at trial the Defendants relied on (1) an internal Teva document created after the May 24, 1994 patent filing date, which compares the molecular weight of batches of copolymer-1 used in Dr. Bornstein's clinical trial with a batch of copolymer-1 having an average molecular weight within the claimed range, and (2) Figure 2 of the patents-in-suit. None of this information, however, was part of the prior art in 1994 and, thus, it cannot be relied on to establish obviousness. *Riverwood Int'l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346, 1354 (Fed. Cir. 2003); *Astra Aktiebolag v. Andrx Pharms.*, 222 F. Supp. 2d 423, 575-78 (S.D.N.Y. 2002), aff'd sub nom. *In re Omeprazole Patent Litig.*, 84 Fed. Appx. 76, 81 (Fed. Cir. 2003) (rejecting obviousness argument based on documents not available to public). Defendants' analysis is clearly based on impermissible hindsight. *See Amgen Inc.*, 580 F.3d at 1363.

Sandoz's Response:

The prior art needed to establish the overlap is the '550 patent itself. Additional prior art is not necessary. The obviousness analysis involves comparing "the differences between the subject matter sought to be patented and the prior art," 35 U.S.C. § 103, and may include considerations of "background knowledge possessed by a person having ordinary skill in the art." *Dow Jones & Co. v. Ablaise Ltd.*, 606 F.3d 1338, 1349 (Fed. Cir. 2010) (*quoting KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. 398, 401 (2007)). A patent may be invalid based on a combination of a single prior art reference and "general knowledge in the field." *Dow Jones*, 606 F.3d at 1353. In fact, during prosecution of the patents-in-suit, the Examiner issued an obviousness rejection over the '550 patent without citing any additional prior art. (PTX 13 at TEV000304142-43.) Teva's claim that an additional prior art reference is required is not supported by the law. Regardless, the molecular weight distributions of Bornstein's copolymer-1 compositions are inherent characteristics, and obviousness may be based upon inherency. *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995) (affirming obviousness of a claimed feature found to be inherent in the prior art).

To the extent Teva argues that there is no overlap between the asserted claims and the ’550 patent, it agrees that the Court may adopt Sandoz’s proposed construction excluding copolymer-1 with a weight average molecular weight above 10 kDa without narrowing the scope of any asserted claim. If the Court does not modify its claim construction to exclude copolymer-1 compositions with a weight average molecular weight of more than 10 kDa, determining overlap merely requires considering whether copolymer-1 with 75% of its molar fraction between 2 and 20 kDa will overlap with copolymer-1 with a weight average molecular weight ranging from 10 to 25 kDa. Dr. Zeiger, testifying as a person of ordinary skill in the art and applying his general knowledge of polymer chemistry, testified in his capacity as an expert in synthetic peptide chemistry, peptide polymer chemistry, and the characterization of the properties of peptide polymers, that the molecular weight distributions of the copolymer-1 described in the ’550 patent would overlap substantially with the copolymer-1 of the patents-in-suit. (Sept. Tr. 867:20-869:9; 873:1-10 (Zeiger).) Dr. Zeiger’s testimony regarding Teva’s internal documents merely provided additional support for his opinions based on his general knowledge.

742. Moreover, even if the claimed molecular weight ranges abutted the prior art, Defendants have failed to prove, as required, that a person of ordinary skill in the art would have had an expectation that a copolymer-1 composition within the claimed average molecular weight range would exhibit the same properties as the prior art high average molecular weight copolymer-1. *See Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985). To establish obviousness, Defendants need to prove by clear and convincing evidence that the person of ordinary skill in the art had a reasonable expectation of success in selecting the claimed molecular weight parameters to make an active copolymer-1 product. *See Genetics Inst. V. Novartis Vaccine & Diagnostics*, No. 2010-1264, 2011 WL 3672474, at *12 (Fed. Cir. Aug. 23, 2011) (despite the overlap in proteins, “the nontrivial differences in the proteins at issue compel the requirement of identifying a reason for the chemical modification”); *Takeda Chem. Indus.*, 492 F.3d at 1360-61; *Key Pharms., Inc. v. Hercon Labs. Corp.*, 981 F. Supp. 299, 313 (D. Del. 1997), aff’d 161 F.3d 709 (Fed. Cir. 1998). Defendants have failed to do so.

Sandoz's Response:

Dr. Rice testified regarding the differences in toxicity profiles one would expect for copolymer-1 compositions found at the upper end of the '808 patent (up to 9.9 kilodaltons peak molecular weight, according to Dr. Grant) and the lower end of the '550 patent (weight average molecular weight of 10 kDa). (Sept. Tr. 1013:8-19.) Dr. Rice specifically noted that to the extent that there was no overlap between the two, she "would expect them to essentially butt up one against the other. So I would not expect any difference in the toxicity profile between the two compositions." (*Id.*) The Court should credit Dr. Rice's testimony.

At the time of the patent application in this case, it was known that those of skill in the art were modifying the molecular weight of copolymer-1. The '550 patent, filed in 1971, taught copolymer-1 with a minimum molecular weight of 10 kDa and a preferred molecular weight range of 20 to 25 kDa. (PTX 26.) The 1974 Teitelbaum abstract taught that copolymer-1 was effective in ranges as low as 17 kDa and up to 50 kDa. (PTX 509 at 1172 noting that copolymer-1 with a molecular weight "lower than 17,000 or higher than 50,000 proved ineffective") By 1987, copolymer-1 with a molecular weight as low as 14 kDa was successfully treating patients suffering from MS. (PTX 31.) Thus, from 1971 to 1974 to 1987, the low end of the preferred or effective range for copolymer-1 went from 20 kDa to 17 kDa to 14 kDa (weight average molecular weights), respectively. The same scientists (Drs. Teitelbaum, Arnon, and Sela) were coauthors and co-inventors of these three publications. (PTX 26, 31, 509.) During this period, copolymer-1 went from being used to treat EAE in guinea pigs ('550 patent) to successfully treating humans suffering from MS (1987 Bornstein). The noticeable decrease in molecular weight over the course of years, combined with increasing usefulness over the same period, is

clear and convincing evidence of a reason to continue to decrease the molecular weight in future experiments.

743. As discussed above, Defendants attempt to rely on the fact that some percentage of copolymer-1 species in the prior art composition would be in the same molecular weight range as copolymer-1 species in the claimed compositions. But, as discussed above, defendants' arguments are based on documents and information not available to the public prior to May 24, 1994. There was nothing in the prior art disclosing or suggesting the overlap relied on by Defendants.

Sandoz's Response:

As discussed in more detail in response to Teva's Proposed FOF No. 741, Dr. Zeiger's testimony regarding Teva's internal documents merely provided additional support for his opinions based on his general knowledge. A patent may be invalid based on a combination of a single prior art reference and "general knowledge in the field." *Dow Jones*, 606 F.3d at 1353.

744. Even if the person of ordinary skill in the art would have known the extent to which the prior art and claimed compositions would overlap, however, Defendants have offered no evidence that the person of ordinary skill in the art would have expected such compositions to have the same or similar biological properties based solely on the degree of overlap in the compositions. *See Genetics Inst.*, 2011 WL 3672474, at *12-13. There was no evidence offered at trial demonstrating that the person of ordinary skill in the art would expect copolymer-1 compositions with overlapping molecular weight distributions would have similar biological properties. (Sept. Tr. (Zeiger) 966:3-967:22.) Indeed, the available evidence suggests just the opposite as the prior art taught that copolymer-1 compositions with lower average molecular weights would likely be ineffective. (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:9; PTX 509 at 1172-73.)

Sandoz's Response:

Sandoz incorporates its responses to Teva's Proposed Findings ¶¶ 738-743. Teva continues to argue that the 1974 Teitelbaum abstract would teach away from using copolymer-1 with a molecular weight below 17 kDa. Teva continues to ignore that 13 years later, despite the so-called "teaching away," the same authors of the 1974 Teitelbaum gave copolymer-1 with a molecular weight of 14 kDa to humans and successfully treated their multiple sclerosis. Dr. Grant's testimony on this topic was not credible. When asked why he thinks the 1974

Teitelbaum abstract still teaches away when the 1987 Bornstein paper had success with a lower molecular weight of 14, Dr. Grant suddenly could not remember one of the most important documents in this case:

> Q. All right. Could we go to PTX-31. And you recognize this as the Bornstein 1987 study, correct?
>
> * * *
>
> A. Yes, I have it.
>
> * * *
>
> Q. It reports on the study that was conducted even earlier than 1987, correct?
>
> A. Yes, I think so.
>
> Q. Let's go to the first paragraph of the Bornstein study -- nope, not in the abstract. There we go.
>
> So despite the warning that you recall seeing of not trying copolymer-1 below 17,000, you'd agree that Dr. Bornstein tested copolymer-1 at 14,000 daltons, correct?
>
> A. That's what's listed there.
>
> Q. Right. And I know that you're not a toxicologist, but I know you've read this study, you would agree that he found the 14,000 dalton molecular weight co-polymer-1, nontoxic, correct?
>
> A. I, frankly, don't recall. It's been a long time since I read this article.

(Sept. Tr. 1543:15-1544:16.) As Dr. Grant was unable to explain why he would still credit the 1974 Teitelbaum abstract over the 1987 Bornstein article, the Court should not credit his testimony that it "teaches away" from using copolymer-1 with a molecular weight of less than 17,000 daltons.

Regarding Dr. Arnon's testimony, Teva merely prompted her to read into the record from the courtroom screen the text of the 1974 Teitelbaum abstract staying that "molecular weight of

either lower than 17,000 or higher than 50,000, and they proved ineffective." (July Tr. 312:23-313:18; PTX 509 at 1172 ("mol wt either lower than 17,000 or higher than 50,000, proved ineffective").) Professor Arnon specifically remembered giving Dr. Bornstein batches of copolymer-1 with a molecular weight of 14 kDa for his "compassionate use" program in the 1980s. It is not credible that if Dr. Arnon believed that copolymer-1 with a molecular weight of 14 kDa was "ineffective," she would give it to patients suffering from multiple sclerosis as part of a compassionate use program. The Court should not credit Teva's "teaching away" theory based on the 1974 Teitelbaum abstract.

745. Defendants have failed to establish that a copolymer-1 composition with an average molecular weight of about 5,000 to 9,000 daltons, or any of the other claimed low average molecular weight ranges (*i.e.*, about 4 to about 9 kilodaltons and 6.25 to 8.4 kilodaltons) were *prima facie* obvious.

Sandoz's Response:

Sandoz has proven by clear and convincing evidence that the copolymer-1 compositions described in the asserted claims of the patents-in-suit were prima facie obvious.

(ii) Copolymer-1 Compositions with the Claimed Molar Fraction Limitations Were Obvious

746. Defendants also contend that copolymer-1 compositions with the claimed molar fraction limitations would have been obvious. Specifically, Defendants contend a copolymer-1 composition with over 75% of its molar fraction within the molecular weight range from about 2 to about 20 kilodaltons, with less than 5% of its molar fraction above 40 kilodaltons, or not more than 2.5% of its molar fraction above 40 kilodaltons, would have been obvious to a person of ordinary skill in the art in May 24, 1994. Nothing in the prior art, however, suggested or taught the claimed molar fraction limitations. Defendants' argument is based on hindsight and unsupported speculation.

Sandoz's Response:

Sandoz addressed these claim limitations above and incorporates its responses to Teva's Proposed Findings of Fact ¶¶ 731-745. Sandoz also incorporates its response in ¶ 116 regarding

Teva's contention that the claims requiring 75% of the copolymer-1 molar fraction between 2 and 20 kDa do not implicate "average molecular weight" determinations.

747. Neither the '550 patent nor the EP '620 Application disclose or suggest copolymer-1 with the specifically claimed molar fraction limitations. (Sept. Tr. (Grant) 1434:13-16, 1439:2-24, 1441:10-25, 1448:17-19; Sept. Tr. (Zeiger) 956:13-958:16.) Neither reference provides any disclosure of the percentage of molecules in any range on a molar fraction basis. (Sept. Tr. (Grant) 1434:13-16, 1439:2-24, 1441:10-25, 1448:17-19; Sept. Tr. (Zeiger) 956:13-958:16.) Neither reference teaches anything about the molecular weight distribution of any polypeptide mixture disclosed in the references. (Sept. Tr. (Grant) 1434:13-16, 1439:2-24, 1441:10-25, 1448:17-19; Sept. Tr. (Zeiger) 956:13-958:16.) Each of the relevant claims relate to a calculation of the molar fractions of copolymer-1, but there was no data presented in the prior art from which a molar fraction could be calculated. (Sept. Tr. (Grant) 1434:13-16, 1439:2-24, 1441:10-25, 1448:17-19; Sept. Tr. (Zeiger) 956:13-958:16.) Nor would a person of ordinary skill in the art have had any reason to make, based on the teachings of the prior art, a copolymer-1 composition with the claimed molar fraction characteristics. There was no evidence presented at trial showing that a person of ordinary skill in the art would have had a reason to focus on or even consider copolymer-1 having any particular molar fraction characteristics. *Takeda Chem. Indus.*, 492 F. 3d 1360-61. Defendants obviousness argument concerning the molar fraction limitations is based entirely on hindsight. *See Amgen, Inc.*, 580 F.3d at 1363.

Sandoz's Response:

Sandoz addressed these claim limitations above and incorporates its responses to Teva's Proposed Findings of Fact ¶¶ 731-745. Sandoz also incorporates its response in ¶ 116 regarding Teva's contention that the claims requiring 75% of the copolymer-1 molar fraction between 2 and 20 kDa do not implicate "average molecular weight" determinations.

748. Like the "average molecular weight" limitations, Defendants again attempt to focus on alleged "overlapping ranges" to support their argument regarding the obviousness of the asserted claims. Defendants argue, based on Figure 2 of the patents-in-suit and the Gad Report discussed above (DTX 1704), that batches prepared using the synthetic processes disclosed in the '550 patent would necessarily have had a large portion of individual polypeptides within the claimed molar fraction ranges. (Sept. Tr. (Zeiger) 987:1-989:29.) First, Defendants point to nothing that supports the argument that batches made according to the prior art '550 method would necessarily meet the molar fraction limitations. And for the reasons set forth above, this argument is legally meritless. *Riverwood Int'l Corp.*, 324 F.3d at 1354; *Astra Aktiebolag*, 222 F. Supp. 2d at 575-78.

Sandoz's Response:

Sandoz addressed these claim limitations above and incorporates its responses to Teva's Proposed Findings of Fact ¶¶ 731-745. Sandoz also incorporates its response in ¶ 116 regarding Teva's contention that the claims requiring 75% of the copolymer-1 molar fraction between 2 and 20 kDa do not implicate "average molecular weight" determinations.

749. Because a person of ordinary skill in the art would not have found obvious a copolymer-1 having the claimed average molecular weight or molar fraction limitations, Defendants have failed to prove by clear and convincing evidence that the following claims are invalid for obviousness on that basis: claim 1 of the '808 patent, claim 1 of the '589 patent, claim 1 of the '847 patent, claims 1-3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, claims 1 and 8 of the '898 patent, and claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent.

Sandoz's Response:

Sandoz has proven by clear and convincing evidence that the following claims are invalid for obviousness: claim 1 of the '808 patent, claim 1 of the '589 patent, claim 1 of the '847 patent, claims 1-3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, claims 1 and 8 of the '898 patent, and claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent.

(iii) The Claimed Process for Making Copolymer-1 Was Obvious

750. Defendants also failed to establish that the process limitations in the patents-in-suit would have been obvious. Defendants failed to prove that the use of Hydrobromic (HBr) acid in acetic acid to cleave peptide bonds in order to control molecular weight would have been obvious to a person of ordinary skill in the art in May 1994. While it was known in the art that HBr in acetic acid could be used for debenzylation, a reaction to remove the benzyl protecting group from an amino acid, such as glutamic acid, there was no prior art disclosure that this reagent could also depolymerize polypeptides to control the average molecular weight.

Sandoz's Response:

Sandoz incorporates its responses to Teva's Proposed Findings ¶¶ 700-714. Sandoz has proven by clear and convincing evidence that each of the process limitations were either previously known or routine modifications to previously known steps. As discussed in detail in Sandoz's Post-Trial Findings of Fact and Conclusions of Law paragraph 191 (and in Sandoz's

Responses to Teva's Proposed Findings of Fact herein), Sandoz proved by clear and convincing evidence that each of the process limitations are either previously known or routine modifications to inherent qualities of previously known steps.

751. As a preliminary matter, the Defendants have failed, as set forth above, to prove by clear and convincing evidence that a person of ordinary skill would have targeted the claimed average molecular weights or molecular weight molar fractions. Without establishing that a person of ordinary skill would have sought to obtain copolymer-1 having these molecular weight characteristics, Defendants have provided no reason that a person of ordinary skill would have been motivated to research or even consider the use of HBr/acetic acid to cleave peptide bonds to control the average molecular weight or molar fraction characteristics of copolymer-1. There is no evidence that a person of ordinary skill in the art would have been motivated to search for some means to decrease the molecular weight of copolymer-1. Defendants' obviousness theory fails for at least this reason.

Sandoz's Response:

Sandoz addresses these claim limitations above, and incorporates its responses to Teva's Proposed Findings ¶¶ 116, 682-694, 700-714, and 731-749. Sandoz has proven by clear and convincing evidence that a person of ordinary skill would have targeted the claimed average molecular weights or molecular weight molar fractions, and that each of the process limitations were either previously known or routine modifications to previously known steps. Sandoz has proven by clear and convincing evidence that the claimed copolymer-1 compositions identified by the recited average molecular weights or molecular weight molar fractions are *prima facie* obvious over the prior art copolymer-1 compositions. As discussed in Sandoz's Post-Trial Findings of Fact and Conclusions of Law paragraph 191 (and in Sandoz's responses to Teva's Proposed Findings), Sandoz proved by clear and convincing evidence that each of the process limitations are either previously known or routine modifications to inherent qualities of previously known steps.

752. Defendants' have also failed to demonstrate by clear and convincing evidence that a person of ordinary skill would have understood at the time the patent application was filed in 1994 that HBr/acetic acid could have been used to cleave peptide bonds in order to control the molecular weight of copolymer-1.

Sandoz's Response:

Sandoz incorporates its responses to Teva's Proposed Findings ¶¶ 700-714. Sandoz has proven by clear and convincing evidence that a person of ordinary skill would have understood at the time the patent application was filed in 1994 that HBr/acetic acid could have been used to cleave peptide bonds in gamma benzyl glutamic acid containing polypeptides, such as those in protected copolymer-1, and thus could be used to control the molecular weight of copolymer-1. As discussed in Sandoz's Post-Trial Findings of Fact and Conclusions of Law paragraph 191 (and in Sandoz's responses to Teva's Proposed Findings), Sandoz proved by clear and convincing evidence that treatment of protected copolymer-1 with HBr/acetic acid to cleave peptide bonds and thus control the weight of copolymer-1, and that adjusting the time and temperature of the reaction conditions would have been a routine step for a person of ordinary skill in the art.

753. The only two references that Drs. Zeiger and Laird introduced regarding the use of HBr in acetic acid for synthesizing copolymer-1 were the '550 patent and the Teitelbaum 1971 article. But neither of these references mention peptide cleavage during the debenzylation step, nor do they mention the use of HBr in acetic acid to control the molecular weight of the resulting copolymer-1 product. (Sept. Tr. (Sampson) 1651:20-1652:11, 1653:4-1655:12; PTX 26, col. 2 ll.53-64; PTX 499 at 243.)

Sandoz's Response:

Sandoz incorporates its responses to Teva's Proposed Findings ¶¶ 700-714.

It is not disputed that neither the '550 patent nor Teitelbaum 1971 specifically mention peptide cleavage during the debenzylation step or adjusting the time and temperature of this step to control the molecular weight of the resulting copolymer-1 product. "[A] reference must be considered not only for what it expressly teaches, but also for what it fairly suggests." *In re Burckel,* 592 F.2d 1175, 1179 (C.C.P.A. 1979). The molecular weight range taught in the '550 patent for copolymer-1 batches, in view of other references such as Idelson 1958, "The Peptides"

or Yaron and Berger, fairly suggests that treatment with HBr in acetic acid would cleave copolymer-1 at the glutamic acid residues. *See* Mylan's proposed findings ¶¶ 290-309; Sept. Tr. 889:10-15 and 913:5-15 (Zeiger).

754. The Defendants attempt to fill this gap in the prior art by relying on references from the 1950's and early 1960's, which suggest, according to Defendants, possible cleavage of peptide bonds following the use of HBr in acetic acid. (Sept. Tr. (Laird) 1139:10-1149:9; Sept. Tr. (Zeiger) 899:12-23, 951:23-15.) Dr. Zeiger, Mylan's expert, testified that the person of ordinary skill in the art would find these references by following a "trail" of six references, that begins with the work of the patentees as described in the '550 patent. (Sept. Tr. (Zeiger) 817:19-818:17, 945:14-952:15.) But these references do not cure the deficiency in the Defendants' prior art case.

Sandoz's Response:

Sandoz incorporates its responses to Teva's Proposed Findings ¶¶ 700-714.

It is disputed that the passage of time somehow invalidates the findings in the references cited by Dr. Zeiger and Dr. Laird. Dr. Sampson relied on a single reference by Merrifield to argue that the prior art "as a whole" did not teach that HBr in acetic acid would be expected to cleave copolymer-1 at the glutamic acid during deprotection of the gamma benzyl group, stating that it was a "seminal" reference. (Sept. Tr. 1644:10-19 (Sampson).) Defendants have cited to at least four references describing partial cleavage of polypeptides upon treatment with HBr that post-date the purportedly seminal Merrifield reference: Yaron & Berger (DTX 1934), Nylund & Miller (DTX 1794), Hayashi (DTX 1781), and "The Peptides" (DTX 1269 at TEV003017895-898). Three of these references, Yaron & Berger, Nylund & Miller, and "The Peptides" describe cleavage of benzyl glutamic acid containing polypeptides upon treatment with HBr/acetic acid. Yet, the Merrifield reference was also from the early 1960s, and predated Yaron and Berger, and Nylund and Miller, and "The Peptides" by two years, and Hayashi by more than 20 years. (PTX-488 at 2149 (Merrifield 1963), DTX-1934 (Yaron and Berger 1965), DTX-1784 (Nylund and Miller 1965); The Peptides (DTX 1269 at TEV003017895-898).)

Dr. Zeiger explained that it is and was routine for a person of ordinary skill to rely on references cited in other prior art, especially when the prior art of interest does not contain sufficient information to carry out the prescribed process. (Sept. Tr. 951:23 – 952:15 (Zeiger).) It is also routine and in fact expected of a person of ordinary skill in the art to study the related publications. Sept. Tr. 847:24-848:6 (Zeiger explaining that a "person of ordinary skill coming into [his] laboratory would be expected to go to … the laboratories that were interested in the subject, and … to follow what they have done subsequently with that reaction").

Dr. Laird testified that a person of ordinary skill in the art would not need to rely on all the cited references to understand that HBr in acetic acid can cause partial cleavage of polypeptides. (Sept. Tr. 1143:1-13; 1148:4-9 (Laird).)

Dr. Laird testified that Ben-Ishai (DTX 1759) treated polypeptides with HBr/acetic acid overnight at room temperature, which falls within the claim limitations 10-50 hours and 20-28 degrees Celsius.

Any of these references, Ben-Ishai 1952, Ben-Ishai 1954, Idelson 1958, Yaron & Berger, Nylund & Miller, Hayashi, or "The Peptides" are properly combined with the '550 patent, alone or in combination with Bornstein 1987 or Bornstein 1991, and render the asserted claims obvious.

755. The evidence shows that a person of skill in the art would not have been motivated to use HBr in acetic acid to cleave the peptide bonds in copolymer-1 polypeptides in order to control the molecular weight of a copolymer-1 sample, even if one assumes that the person of skill were motivated to decrease the average molecular weight of copolymer-1.

Sandoz's Response:

Sandoz incorporates its responses to Teva's Proposed Findings ¶¶ 700-714. Sandoz has proved by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to use HBr in acetic acid to cleave the peptide bonds in protected copolymer-1

poplypeptides to control its resultant molecular weight, and to achieve the claimed molecular weights.

756. HBr in acetic acid was used as a step in the *synthesis* of polypeptides, where the cleavage of the polypeptide chain would viewed negatively as something that would need to be minimized or avoided altogether. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1655:13-1656:17, 1683:16-19; PTX 488.) The prior art relied on by defendants shows that the alleged cleavage disclosed was, at best, an undesirable side reaction, not something that would be viewed as a tool to be used to decrease the molecular weight of copolymer-1. (Sept. Tr. (Sampson) 1642:9-20, 1655:13-1656:4; Sept. Tr. (Laird) 1139:22-1140:8; 1154:2-1155:12.)

Sandoz's Response:

Sandoz incorporates its responses to Teva's Proposed Findings ¶¶ 700-714.

Teva's citation to Dr. Laird's testimony is misleading as he testified that a person of skill in the art would be "able to use the knowledge of peptide cleavage under those conditions to control peptide cleavage if that is what you wanted to do." (Sept. Tr. 1155:7-12.) Dr. Laird testified that if a person of skill in the art wanted to make copolymer-1 of a lower molecular weight they would have been motivated to use HBr in acetic acid as it had previously been used in manufacturing copolymer-1, and they would have expected it to partially cleave the peptide bonds. (Sept. Tr. 1143:14 – 1144:11; 1155:13 -23.)

Sandoz has proved by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to use HBr in acetic acid to cleave the peptide bonds in protected copolymer-1 poplypeptides to control its resultant molecular weight, and to achieve the claimed molecular weights.

757. The opinions of Defendants' experts are based on hindsight. Dr. Laird and Dr. Zeiger cite to references reporting that the use of HBr in acetic acid for debenzylation could potentially result in some peptide cleavage. (Sept. Tr. (Laird) 1139:10-1142:9.) But neither Dr. Laird nor Dr. Zeiger offered any explanation why the person of ordinary skill in the art would seek to use the debenzylation reaction, or HBr in acetic acid, to cleave the peptides during the process for making copolymer-1. (Sept. Tr. (Laird) 1155:4-23; Sept. Tr. (Zeiger) 817:19-818:17, 945:14-952:15.)

Sandoz's Response:

Sandoz incorporates its responses to Teva's Proposed Findings ¶¶ 700-714 and 756.

Both Dr. Laird and Dr. Zeiger offered explanations for why a person of skill in the art would seek to use HBr in acetic acid to cleave peptides when making copolymer-1. Dr. Zeiger testified that under the conditions cited in Teitelbaum 1971 for preparing copolymer-1 compositions (overnight at room temperature), which the '550 patent utilized, a person of ordinary skill in the art would have expected some peptide bond cleavage to occur. (Sept. Tr. 862:6-19 (Zeiger).) Thus, the only issue is whether that person would have been motivated to vary the time and temperature to obtain a molecular weight range that overlaps or abuts the '550 patent. Dr. Zeiger testified that varying time and temperature are routine variables and this is nothing more than routine optimization, which is not a patentable invention. (Sept. Tr. 853:21-854:15 (Zeiger).). Dr. Laird testified that a person of skill in the art would be "able to use the knowledge of peptide cleavage under those conditions to control peptide cleavage if that is what you wanted to do." (Sept. Tr. 1155:7-12.) Dr. Laird also testified that if a person of skill in the art wanted to make copolymer-1 of a lower molecular weight they would have been motivated to use HBr in acetic acid as it had previously been used in manufacturing copolymer-1, and they would have expected it to partially cleave the peptide bonds. (Sept. Tr. 1143:14 – 1144:11; 1155:13 -23.)

758. Dr. Zeiger's testimony that the person of ordinary skill in the art would ignore the Merrifield 1963 article because it did not directly address whether HBr in acetic acid could cleave a specific type of peptide – a gamma-benzyl glutamic acid containing peptide – is not credible. That testimony is directly refuted by the testimony of Dr. Laird that the person of ordinary skill in the art would not focus on benzyl containing peptide bonds because all peptide bonds are closely similar. (Sept. Tr. (Laird) 1151:18-25.) Moreover, Dr. Zeiger's focus on gamma-benzyl glutamic acid containing peptides is based on hindsight. Dr. Zeiger did not provide any basis for the person of ordinary skill in the art to conclude that gamma-benzyl glutamic acid bonds is the site of cleavage in protected copolymer-1 polypeptides treated with HBr in acetic acid, nor did Dr. Zeiger identify any reason that a person of skill in the art would

have focused on the gamma-benzyl glutamic acid bond other than the fact that it is found in copolymer-1.

Sandoz's Response:

Sandoz incorporates its responses to Teva's Proposed Findings ¶¶ 700-714, 754 and 756.

Dr. Zeiger presented detailed testimony on how a person of ordinary skill would explain the variation in molecular weight observed in the '550 patent specifically as it relates to copolymer-1. That person would have understood that the variation in molecular weight would likely be due to peptide bond cleavage, specifically at the glutamic acid because peptide bond cleavage by HBr in acetic acid had been previously described in analogous literature for peptides containing this protecting group. *See* Mylan's proposed findings of fact and conclusions of law ¶¶298-309. This is not a hindsight analysis. This analysis applies the prior art, the '550 patent, and describes what it fairly teaches to a person of ordinary skill in the art in view of other analogous art. *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). Dr. Zeiger explained that the Merrifield reference does not discuss peptide bond cleavage because the peptide bond cleavage requires a side-chain protecting group, which none of the amino acids in the peptides described in Merrifield's article contain. (Sept. Tr. 1711:16-24 (Zeiger).) This analysis relates to the protecting group present, not the actual amino acid. Thus, Dr. Laird's testimony (Sept. Tr. 1151:18-25), does not contradict Dr. Zeiger's analysis.

759. Certain asserted claims of the patents-in-suit include specific time and temperature limitations. Those include claims 2 and 3 of the '898 patent and claims 2 and 3 of the '430 patent. Defendants failed to prove that the person of ordinary skill in the art would have been motivated to select or would have selected any particular time and temperature for the HBr/acetic acid step or that the person of ordinary skill in the art would have had any expectation that selecting a particular time and temperature for performing the HBr in acetic acid deprotection reaction would affect the resulting average molecular weight or molar fractions of the copolymer-1 product. (Sept. Tr. (Sampson) 1644:20-1647:10; 1685:13-1686:18; PTX 488 at 2151, 2153; DTX 1934 at 318.) Thus, Defendants have failed to establish that the person of ordinary skill in the art would have selected a time of 10-50 hours and a temperature of 20-28 degrees C or a time of about 17 hours and a temperature of about 26 degrees C for the reaction of protected copolymer-1 with HBr in acetic acid, as recited in claims 2 and 3 of the '898 patent

and claims 2 and 3 of the ’430 patent. Defendants have failed to demonstrate the obviousness of these claims by clear and convincing evidence.

Sandoz’s Response:

Sandoz incorporates its responses to Teva’s Proposed Findings ¶¶ 700-714, 754 and 756. Claims 3 of the ’898 and ’430 patents have not been asserted against Sandoz. Sandoz proved by clear and convincing evidence that it would have been obvious to a person of ordinary skill in the art in May 1994 to select the recited time and temperature conditions to arrive at a particular average molecular weight or molar fraction of copolymer-1 as this is nothing more than routine optimization of two common chemical reaction variables. Dr. Sampson agreed, for example, that the Ben-Ishai article teaches deprotecting in HBr/acetic acid at 20 to 26 degrees Celsius for 10-20 hours. (Sept. Tr. 1678:4-23 (Sampson).) She also testified that deprotection and peptide cleavage occur in the same step of the process, in the same time and temperature range as the prior art process. (Sept. Tr. 1682:1-11 (Sampson).)

760. Claims 1-3 of the ’898 patent, which require obtaining a “predetermined molecular weight profile” through the use of HBr in acetic acid would similarly not have been obvious. Defendants have not established by clear and convincing evidence that a person of ordinary skill would have been motivated to set a predetermined molecular weight profile for copolymer-1 or that it would have been obvious that such a molecular weight profile could be controllably achieved through treatment of protected copolymer-1 with HBr in acetic acid.

Sandoz’s Response:

Sandoz incorporates its responses to Teva’s Proposed Findings ¶¶ 700-714, 754 and 756. Claim 3 of the ’898 patent has not been asserted against Sandoz.

Sandoz proved by clear and convincing evidence that one of skill in the art would have been motivated to set a predetermined molecular weight profile and it would have been obvious to obtain that profile through variations of the time and temperature of the treatment with HBr in acetic acid. *See, also,* Mylan’s proposed findings of fact and conclusions of law ¶¶ 140-144, and 425-433.

761. None of the prior art references render obvious the use of HBr in acetic acid in order to control the average molecular weight or the molecular weight distribution of copolymer-1 or its intermediary, TFA-copolymer-1. Because Defendants have failed to prove that the process limitations requiring such a reaction would have been obvious, none of the claims of the patents-in-suit are invalid for obviousness on this basis.

Sandoz's Response:

Sandoz incorporates its responses to Teva's Proposed Findings ¶¶ 700-714. Sandoz has proved by proved by clear and convincing evidence that the prior art process for making copolymer-1 consisted of using the identical reagents at the same time and temperature conditions claimed in the asserted patents, and that a person of ordinary skill in the art would have found it routine to optimize this process step in order to control the average molecular weight or the molecular weight distribution of copolymer-1.

(iv) Secondary Considerations

762. Secondary considerations further support the conclusion that the asserted claims are non-obvious. *See Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966); *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010). When present, secondary considerations "may often be the most probative and cogent evidence [of non-obviousness] in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Evidence of secondary considerations must be considered if present. *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1343 (Fed. Cir. 2010). These secondary considerations include commercial success of the claimed invention; the invention's satisfaction of a long-felt need in the art; the failure of others to solve the problem addressed by the invention; unexpected results and copying of the invention.

Sandoz's Response:

While they must be considered, if present, "evidence of secondary considerations does not always overcome a strong prima facie showing of obviousness." *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1333 (Fed. Cir. 2009).

(1) Commercial Success

763. The commercial success of an embodiment of the claimed invention is strong evidence of its non-obviousness. *See Graham*, 383 U.S. at 17; *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 957 (Fed. Cir. 1997) (evidence of commercial success may be "highly probative of the issue of nonobviousness"). To establish commercial success, a patentee must show significant sales in the relevant market and a nexus to the claimed invention (that the

success was due to the patented invention). *Rolls-Royce, PLC v. United Tech. Corp.*, 603 F.3d 1325, 1340 (Fed. Cir. 2010). "[I]f the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." *Brown & Williamson Tobacco Corp. v. Phillip Morris, Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). A successful product is "coextensive" with the claimed invention when it is commensurate in scope with the patented invention, as opposed to only a "component of a commercially successful" product. *Mitsubishi Chem. Corp. v. Barr Labs, Inc.*, 718 F. Supp. 2d 382, 437 (S.D.N.Y. 2010) (finding a pharmaceutical formulation "coextensive" with the asserted claims where it was an "inextricable and essential part of what doctors are prescribing" and "not a part that can be separated out from the remainder of the product"), *aff'd*, No. 2010-1432, 2011 WL 3288394 (Fed. Cir. Aug. 2 2011).

Sandoz's Response:

Teva failed to establish unexpected results or to show a nexus between its sales of Copaxone and the claimed improvement over the copolymer-1 used in the Bornstein BR-1 clinical trials. (*See* Sandoz's Responses to ¶¶ 715-730.)

764. The significant sales and the growing market share of Copaxone® constitutes commercial success, and is further evidence of the non-obviousness of the asserted claims. *See Tec-Air, Inc. v. Denso Mfg. Michigan, Inc.*, 192 F.3d 1353, 1361 (Fed. Cir. 1999) ("Although sales figures coupled with market data provide stronger evidence of commercial success, sales figures alone are also evidence of commercial success."); *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 21 F. Supp. 2d 366, 374 (S.D.N.Y. 1998), *aff'd*, 231 F.3d 1339 (Fed. Cir. 2000) (finding that $1 billion in annual sales of Pepcid® despite pressure from competitors is clearly a sign of commercial success).

Sandoz's Response:

Teva failed to establish unexpected results or to show a nexus between its sales of Copaxone and the claimed improvement over the copolymer-1 used in the Bornstein BR-1 clinical trials. (*See* Sandoz's Responses to ¶¶ 715-730.)

765. The unrebutted record evidence also establishes that Copaxone® meets the limitations of at least one claim of each of the patents-in-suit. Clearly the claimed inventions are "an inextricable and essential part of what doctors are prescribing" when they prescribe Copaxone®. Copaxone® is, therefore, coextensive with the asserted claims. *See Mitsubishi Chem. Corp.*, 718 F. Supp. 2d at 437. Because Copaxone® embodies and is coextensive with the asserted claims, a nexus between commercial success and the patented invention is presumed. *See, e.g.*, *Rolls-Royce, PLC*, 603 F.3d at 1340; *Mitsubishi Chem. Corp.*, 718 F. Supp. 2d at 437-40.

Sandoz's Response:

Whether Copaxone is covered by the claims depends on, among other things, whether it satisfies the 6:2:5:1 claim limitation. If not, then there is no nexus between sales of Copaxone and nonobviousness.

Even if a nexus were presumed, Dr. Greene testified, without contradiction, that there are no clinically significant differences between Bornstein's copolymer-1 and Teva's Copaxone. (Sept. Tr. 1370:17-21.) Dr. Pinchasi likewise agreed that there was no evidence of a difference in side effects between the Bornstein and Johnson studies. (*E.g.*, July Tr. 265:18-267:1 (Pinchasi).) Teva urged the FDA to approve Copaxone based on the success of the Bornstein BR-1 studies. (July Tr. 268:23-269:12.) The FDA accepted Teva's arguments that the BR-1 material was sufficiently representative of what Teva would market such that the Bornstein data could be relied upon to show safety and efficacy. (Sandoz's Opening FFCOL ¶¶ 181, 193-203.)

The only difference between the material used in the Bornstein BR-1 trials and the material commercially sold as Copaxone is that Copaxone had FDA approval, whereas the Bornstein material did not. Regulatory approval is not a patented feature of Copaxone. Because Copaxone's commercial success is attributable to a non-patented feature, Sandoz meets its burden, to the extent it had one, to show that the commercial success is the result of a factor other than the claimed features.

To the extent that Teva argues that Copaxone has a lower molecular weight than the material used in the Bornstein clinical trials, there is conflicting evidence on that issue. Teva's documents show that some of the copolymer-1 used in the Bornstein Br-1 clinical trials had a peak molecular weight as low as 10,350 and perhaps as low as 8,000 daltons. (Sandoz FOF ¶ 200.)

766. When a patentee establishes a presumptive *prima facie* nexus based upon the success of a commercial embodiment of the claimed inventions, the burden shifts to the challenger to demonstrate that the commercial success results from a factor other than the invention. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). Defendants have made no such showing. *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 679 (Fed. Cir. 1988); *Brown & Williamson*, 229 F.3d at 1130 ("The presumed nexus cannot be rebutted with mere argument; evidence must be put forth."). Thus, a nexus exists between Copaxone®'s commercial success and the claimed inventions.

Sandoz's Response:

See Sandoz's response to Teva's Proposed Finding of Fact No. 765.

767. Even if some rebuttal evidence had been presented, the record reflects an adequate nexus between Copaxone® and the features of the claimed invention. Dr. Lisak explained that his prescriptions for Copaxone® have increased over time because of the clinical advantages of the product, and his testimony was consistent with the record evidence that the usage of Copaxone® has grown over time. (Sept. Tr. (Lisak) 119:8-120:9; Sept. Tr. (Congleton) 50:12-51:2.) This evidence demonstrates a nexus between the commercial success of Copaxone® and the properties of the patented inventions. *See Mitsubishi Chem. Corp.*, 718 F. Supp. 2d 382 at 438.

Sandoz's Response:

Dr. Lisak testified that there was no nexus between his prescriptions for copolymer-1 and any purported relationship between molecular weight and toxicity. (Sept. Tr. 163:21-24.)

(2) Long-felt, Unmet Need

768. "Recognition of need, and difficulties encountered by those skilled in the art, are classical indicia of non-obviousness." *In re Dow Chem. Co.*, 837 F.2d 469, 472 (Fed. Cir. 1998). "The existence of an enduring, unmet need is strong evidence that the invention is novel, not obvious, and not anticipated. If people are clamoring for a solution, and the best minds do not find it for years, that is practical evidence—the kind that can't be bought from a hired expert, the kind that does not depend on fallible memories or doubtful inferences—of the state of knowledge." *In re Manhurkar*, 831 F. Supp. 1354, 1378 (N.D. Ill. 1993), *aff'd*, 71 F.3d 1573 (Fed. Cir. 1995). Where there is a long-standing need in the medical community for a safe and effective treatment for a particular disease, an invention that fulfills that need is often deemed non-obvious. *See Eli Lilly & Co. v. Zenith Goldline Pharmas., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006) ("The record shows a long-felt need for a safer, less toxic, and more effective clozapine-like drug."); *Pfizer, Inc. v. Ranbaxy Labs Ltd.*, 405 F. Supp. 2d 495, 518 (D. Del. 2005) (finding that, despite other products available on the market, "Lipitor® satisfied a long-felt need in the medical community to provide patients with more effective statins to help them achieve their LDL goals"), *rev'd on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006).

Sandoz's Response:

See response to Teva's Finding of Fact No. 769.

769. The facts show that by 1994, there remained a long, unmet need for an effective, safe and tolerable disease-modifying treatment for RRMS. (Sept. Tr. (Lisak) 125:25-127:14.) The introduction of Copaxone® fulfilled long-felt unmet needs for: (a) an additional effective, safe and tolerable treatment for RRMS; (b) a treatment for RRMS with a unique mechanism of action that worked differently than interferons; and (c) a treatment that had a milder side effect profile than the interferons. (Sept. Tr. (Lisak) 125:25-128:25.) Copaxone®'s fulfillment of each of these long-felt needs are secondary considerations that further support a finding of non-obviousness concerning the asserted claims of the patents-in-suit. *See Eli Lilly & Co*, 471 F.3d at 1380 (Fed. Cir. 2006); *Pfizer, Inc.*, 405 F. Supp. 2d at 518.

Sandoz's Response:

Any long-felt need was met when Dr. Bornstein's patients were effectively treated for MS with copolymer-1 in the 1980s. (PTX 31.) Betaseron (an interferon) was launched in the United States in July 1993 – one year before Teva applied for the patents-in-suit. (Sept. Tr. 46:23-47:1 (Congleton); Lisak Slide 9.) Teva says that in 1994, there was an "unmet" need for the invention. The demand for something other than Betaseron was not "long felt," as Betaseron had only been on the market ten months when Teva filed its patent. (Sept. Tr. 46:23-47:1 (Congleton); Lisak Slide 9.) By the time Copaxone came to the market, other MS drugs, such as Avonex had entered the market. (*Id.* (noting that Avonex entered the market in 1996).)

(3) Failure of Others

770. The repeated failure of others to solve a problem addressed by an invention lends further support to the invention's nonobviousness. *See Graham*, 383 U.S. at 17 (the "failure of others" is a secondary consideration of non-obviousness). In the pharmaceutical industry, the failure of others to develop a safe and effective drug often supports the nonobviousness of a drug that finally achieves success. *See, e.g.*, *Yamanouchi Pharm. Co.*, 21 F. Supp. 2d at 374 (stating that the evidence showing that "the pharmaceutical industry at large was attempting to improve upon existing [anti-ulcer] drugs with only a small number of producers coming close to success" supports a finding of nonobviousness); *Eli Lilly & Co. v. Zenith Goldline Pharm.*, 364 F. Supp. 2d 820, 832 (S.D. Ind. 2005), *aff'd*, 471 F. 3d 1369 (Fed. Cir. 2006).

Sandoz's Response:

See Sandoz's response to Teva's Proposed Findings of Fact Nos. 724-729.

771. Evidence was presented at trial of drugs that showed initial promise for the treatment of MS, but that failed because of lack of efficacy or significant side effects. (Sept. Tr. (Lisak) 131:14-136:19; PTX 99; PTX 523; PTX 538; PTX 591; PTX 605; PTX 616; PTX 617; PTX 623; PTX 626; PTX 627; PTX 644.) There is undoubtedly an economic incentive to develop drugs to treat MS, yet the evidence of numerous failed therapies demonstrates the difficulty in developing effective therapies for MS. (Sept. Tr. (Lisak) 135:22-136:10; PTX 644 at 184.) Copaxone®'s success in light of these failed attempts provides further support for the non-obviousness of the asserted claims. *See Yamanouchi Pharm. Co.*, 21 F. Supp. 2d at 374; *Eli Lilly & Co.*, 364 F. Supp. at 832.

Sandoz's Response:

See Sandoz's response to Teva's Proposed Findings of Fact Nos. 724-729.

(4) Unexpected Results

772. Unexpected superior properties or advantages of an invention are another secondary consideration of nonobviousness. *Procter & Gamble Co. v. Teva Pharma. USA, Inc.*, 566 F.3d 989, 993 (Fed. Cir. 2009). As the Federal Circuit has explained, "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997). Unexpected results may be shown with proof that (1) there is a difference between the results obtained and the closest prior art, and (2) the differences would not have been expected by one skilled in the art at the time of the invention. *Procter & Gamble Co.*, 566 F.3d at 997-98. The unexpected reduced toxicity of a drug as tested on animal models supports a finding of non-obviousness. *See, e.g.*, *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 536 F. Supp. 2d 476, 477-78, 496-97 (D. Del. 2008) (unexpected reduced toxicity demonstrated using a "short term toxicity screen" with rats), *aff'd*, 566 F.3d 989 (Fed. Cir. 2009); *Takeda Chem. Indus.*, 417 F. Supp. 2d at (unexpected lower toxicity demonstrated in mice and rat testing, as well as an *in vitro* chick lens assay).

Sandoz's Response:

Teva cites some non-binding cases for the proposition that reduced toxicity of a drug as tested on animal models supports a finding of non-obviousness. Those cases are inapplicable here, as the toxicity of copolymer-1 was found not to be toxic in animals well before Teva filed its patent application in 1994. (*E.g.*, PTX 31 at 408 ("Cop 1 . . . is not toxic in animals. . . . Cop 1 is also nontoxic during short-term and longer-term (three to six months) administration in mice, rabbits, and dogs. . . .").) Because copolymer-1 was already "not toxic" in animals, its toxicity could not be reduced. In the context of humans, Dr. Arnon testified that she is not aware

of anyone ever testing whether reducing the molecular weight of copolymer-1 reduces side effects in humans. (July Tr. 346:22-25.)

773. The record establishes that low molecular weight copolymer-1 was unexpectedly superior to the prior art copolymer-1. The *in vivo* and *in vitro* toxicity data generated by the Weizmann scientists and Teva showed that the claimed lower molecular weight copolymer-1 had unexpectedly lower toxicity than higher molecular weight copolymer-1 batches. (*See, e.g.*, July Tr. (Arnon) 333:18-334:2; July Tr. (Pinchasi) 32:1-6, 33:6-35:5, 46:21-47:8, 48:4-49:11, 55:7-58:21, 59:1-70:11; PTX 54; PTX 53; PTX 40.) Dr. Baird considered these and other data, and explained that they established a trend of decreasing toxicity with decreasing molecular weight. (July Tr. (Baird) 603:20-605:18, 607:10-608:15; PTX 34T; PTX54; PTX 887 at 44.) Dr. Pinchasi also described the existence of this trend and stated that the relationship between molecular weight and toxicity was "very unexpected" since nothing in the literature pointed the development team in that direction. (July Tr. (Pinchasi) 32:1-6.) Defendants' toxicology expert, Dr. Susan Rice, agreed that one of skill in the art would have no expectation with respect to how lowering the molecular weight of copolymer-1 would impact toxicity. (Sept. Tr. (Rice) 1046:25-1047:7.) The lower toxicity of the low molecular weight copolymer-1 thus is an unexpected result that provides further support for a finding of nonobviousness regarding the asserted claims. *See Procter & Gamble Co.* 536 F. Supp. 2d at 477-78; *Takeda Chem. Indus., Ltd.*, 417 F. Supp. 2d at 357-58, 385-86.

Sandoz's Response:

Teva has not shown that its copolymer-1 was "unexpectedly superior" to the prior art copolymer-1. Sandoz has briefed this extensively. (*See, e.g.*, Sandoz's Opening FFCOL ¶¶ 229-234 and other responses herein.)

774. Teva's experience with TV-5010, a high molecular weight version of copolymer-1, provides further evidence of the unexpectedly superior toxicity profile of low molecular weight copolymer-1. The record shows that Teva dropped the TV-5010 project due to safety problems, including serious injection site reactions and deaths in animals, discovered during toxicology studies. (July Tr. (Pinchasi) 105:25-106:11, 110:11-111:9; PTX 158 at TEV002207062.) These results reinforce the trend observed by Teva of increasing molecular weight and increasing toxicity, and they provide further support for the unexpected results seen with low molecular weight copolymer-1. *Genetics Institute, LLC*, 2011 WL 3672474, at *14 ("[I]t would be error to prohibit a patent applicant or patentee from presenting relevant indicia of nonobviousness, whether or not this evidence was available or expressly contemplated at the filing of the patent application."); *In re Chu*, 66 F.3d 292, 298-99 (Fed. Cir. 1995) (noting that evidence supporting non-obviousness need not be contained within the specification).

Sandoz's Response:

Teva's decision to try a higher molecular weight version of copolymer-1 after supposedly discovering that lower molecular weight copolymer-1 was less toxic proves, if anything, that Teva, including Dr. Pinchasi, did not believe that its lower molecular weight version of copolymer-1 was unexpectedly different than the prior art. (*See* Sandoz's Responses to ¶¶ 180-183.)

(5) Copying

775. Additional evidence of the non-obviousness of the asserted claims is the deliberate copying of the inventions by both Defendants. *See Arkie Lures*, 119 F.3d at 957 (evidence of copying may be "highly probative of the issue of nonobviousness"); *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1328-29 (Fed. Cir. 2009); *Crocs, Inc.*, 598 F.3d at 1311 ("[c]opying may indeed be another form of flattering praise for inventive features"). "The fact that copying is likely to be present in many Hatch-Waxman Act cases does not allow the court to ignore the copying as evidence of nonobviousness" and in fact, in the field of new drug design, "the very need for copying results from and emphasizes the unpredictability of medicinal chemistry." *Eli Lilly & Co. v. Zenith Goldline Pharma.*, No. IP 99-38, 2001 WL 1397304, at *14 (S.D. Ind. Oct. 29, 2001); *see also Sanofi-Aventis Deutschland GmbH v. Glenmark Pharma., Inc.*, No. 07-cv-5855, 2011 WL 383861, at *9 (D. N.J. Feb. 3, 2011) ("Copying, as secondary considerations evincing non-obviousness, is [an] important part of demonstrating non-obviousness even in a pharmaceutical patent case against an ANDA filer because an ANDA filer is not *required* to copy.").

Sandoz's Response:

(*See* Sandoz's Opening FFCOL ¶¶ 239, 248; *see also* Sandoz's Responses to ¶¶ 23, 288-300.)

776. [redacted] Mani Iyer, Momenta's Associate Director of Drug Substance Manufacturing and Development testified that Momenta followed Teva's patents on making low molecular weight copolymer-1. (PTX 960 (Iyer Dep.) at 5:18-6:11, 128:18-130:17.) The time and temperature Momenta originally used for its debenzylation step were copied directly from the '808 patent. (PTX 960 (Iyer. Dep.) at 146:25-148:11. [redacted] The import of such copying on non-obviousness merits even greater

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weight in view of Defendants' failed attempts to develop alternative processes. *Advanced Display Systems, Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285-86 (Fed. Cir. 2000) (finding that "wholesale copying of the claimed invention" despite attempts to design around is evidence of non-obviousness). Further, it is clear that the defendants were aware of the '550 patent and its disclosure of higher molecular weight copolymer-1, but they chose to submit to the FDA applications to market a lower molecular weight copolymer-1 falling within the scope of the asserted claims. *Eli Lilly & Co.*, 2001 WL 1397304, at *14; *Janssen Pharmaceutica N.V. v. Mylan Pharma., Inc.*, 456 F. Supp. 2d 644, 671 (D. N.J. 2006) ("undisputed copying" by Mylan, among other ANDA filers, supported nonobviousness). This evidence of copying further supports a finding that the claims of the patents-in-suit are not obvious.

Sandoz's Response:

Sandoz and Momenta's goal is to bring a generic version of Copaxone to the market, not to copy Teva's patents. Teva points to Sandoz's and Momenta's early development efforts, which are protected by the safe harbor provisions of 35 U.S.C. § 271(e)(1), and ignores that the current version of Sandoz's process of making its product is different than what is described in the patents. (*See* Sandoz's Opening FFCOL ¶¶ 239, 248; *see also* Sandoz's Responses to ¶¶ 23, 288-300.)

XI. CONCLUSION

The Court should conclude that Sandoz does not infringe the asserted claims, the asserted claims are invalid, and the asserted patents are unenforceable.

Dated: October 24, 2011

New York, New York

By: ______________________

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